

**INFLUENCES OF AFFECTIVE PROCESSING AND EMOTIONAL CONTEXT ON  
NEURAL ACTIVATION DURING COGNITIVE CONTROL FROM ADOLESCENCE  
THROUGH ADULTHOOD**

by

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Emotion processing and cognitive control show marked development through adolescence, during which these systems have an enhanced effect on decision-making. Past studies have shown increased engagement of emotion-related regions in adolescents compared to adults during tasks eliciting different moods on a trial-by-trial basis, but few studies have examined state-related effects of emotion. Here, we investigated age-related changes in effects of emotional state on cognitive control using background connectivity, in which task-based signals are removed from fMRI data to examine spontaneous background fluctuations in neural activity.

50 participants completed a standard antisaccade fMRI task in a 3T scanner. Each trial included a positive, negative, or neutral sound that played before and during each trial. All subjects also completed a 5-minute resting state scan in the same session. Outside of the scanner, all subjects completed valence and arousal ratings of all sounds. Data were preprocessed using a standard preprocessing pipeline including wavelet despiking. Resting state data additionally underwent bandpass filtering and global signal regression. To obtain background connectivity data, task-related effects were estimated and then removed using multiple linear regression.

Across subjects, latency significantly decreased with increasing age in negative trials, while the percentage of correct responses significantly increased in silent trials. The negative sounds were also perceived as more “arousing” in adults compared to adolescents. Using a bilateral amygdala seed to examine whole-brain background connectivity, increasing age was associated

with increasing connectivity to brain regions with the dorsal attention network and salience network, among others. Resting state connectivity analyses revealed no significant age-related changes in amygdala background connectivity with these brain regions.

This study suggests that negative affective stimuli may be more salient to adults, which may have a beneficial effect on their behavioral performance. Additionally, this may indicate increased emotional awareness in adults, as compared to adolescents, which may be driven by the development of connectivity between the amygdala and various cortical regions through this period.

## TABLE OF CONTENTS

<b>1.0 SPECIFIC AIMS .....</b>	<b>1</b>
<b>2.0 BACKGROUND .....</b>	<b>7</b>
<b>2.1 Adolescent Development .....</b>	<b>7</b>
<b>2.2 Adolescent Development of Inhibitory Control.....</b>	<b>8</b>
<b>2.3 Development of Emotion Reactivity, Perception, and Regulation During Adolescence .....</b>	<b>9</b>
<b>2.4 Interactions Between Emotion and Inhibitory Control.....</b>	<b>11</b>
<b>2.4.1 Negative Emotion .....</b>	<b>11</b>
<b>2.4.2 Positive Emotion.....</b>	<b>13</b>
<b>2.5 Background Connectivity .....</b>	<b>15</b>
<b>2.6 The Current Study .....</b>	<b>16</b>
<b>3.0 METHODS .....</b>	<b>17</b>
<b>3.1 Participants .....</b>	<b>17</b>
<b>3.2 fMRI Task Design.....</b>	<b>17</b>
<b>3.3 MR Data Acquisition.....</b>	<b>19</b>
<b>3.4 Eye Tracking Data Acquisition .....</b>	<b>20</b>
<b>3.5 Eye Tracking Data Scoring.....</b>	<b>20</b>
<b>3.6 fMRI Preprocessing.....</b>	<b>21</b>
<b>3.7 Data Analysis .....</b>	<b>22</b>
<b>3.7.1 Aim One .....</b>	<b>22</b>
<b>3.7.2 Aim Two.....</b>	<b>23</b>

3.7.2.1 First Level Analysis .....	23
3.7.2.2 Second Level Analysis .....	23
3.7.3 Aim Three .....	24
3.7.3.1 First Level Analysis .....	24
3.7.3.2 Second Level Analysis .....	25
<b>4.0 RESULTS .....</b>	<b>26</b>
<b>4.1 Aim One.....</b>	<b>26</b>
4.1.1 Percentage of Correct Responses.....	26
4.1.2 Response Latency .....	27
4.1.3 Arousal and Valence Ratings .....	27
<b>4.2 Aim Two .....</b>	<b>28</b>
4.2.1 fMRI Task Activation.....	28
<b>4.3 Aim Three.....</b>	<b>29</b>
4.3.1 Background Connectivity.....	29
<b>5.0 DISCUSSION .....</b>	<b>31</b>
<b>6.0 CONCLUSION .....</b>	<b>35</b>
<b>APPENDIX A TABLES .....</b>	<b>36</b>
<b>APPENDIX B FIGURES .....</b>	<b>39</b>
<b>BIBLIOGRAPHY .....</b>	<b>45</b>

## LIST OF TABLES

Table 1: Clusters from Voxelwise Analysis of Task Activation - Condition x TR Contrast ( $p < 0.001$ voxelwise, $p < 0.05$ corrected) .....	36
Table 2: Clusters from Voxelwise Analysis of Task Activation - Age x TR Contrast ( $p < 0.001$ voxelwise, $p < 0.05$ corrected) .....	37
Table 3: Clusters from Voxelwise Analysis of Age Effects on Amygdala Background Connectivity ( $p < 0.005$ voxelwise, $p < 0.05$ corrected) .....	38



## LIST OF FIGURES

Figure 1: Histogram showing age distribution of task subject pool, grouped by gender. ....	39
Figure 2: Histogram showing age distribution of rest subject pool, grouped by gender. ....	39
Figure 3: Diagram of affective antisaccade task design. ....	40
Figure 4: Examples of positive, negative, and neutral sounds included in task. ....	40
Figure 5: Graphical representation of the arousal-by-valence relationship. ....	41
Figure 6: Line graph depicting the relationship between age and percentage of correct responses, separated by task condition and controlling for gender. ....	41
Figure 7: Line graph illustrating the association between age and response latency for correct trials, separated by task condition and controlling for gender. ....	42
Figure 8: Line graph representing the relationship between age and individual arousal ratings for sounds included in the task, separated by task condition and controlling for gender. ....	43
Figure 9: Line graph showing the association between age and individual valence ratings for sounds included in this task, separated by task condition and controlling for gender. ....	43
Figure 10: A whole-brain voxelwise analysis examining the effects of condition, TR, age, and gender. ....	44

## 1.0 SPECIFIC AIMS

Adolescence is a period of heightened reactivity to affective context (Guyer, Silk, & Nelson, 2016) in parallel with still-maturing cognitive control (Luna, Marek, Larsen, Tervo-Clemmens, & Chahal, 2015) resulting in increased influence of affective processes over cognitive ones (Shulman et al., 2016). This increased reactivity to affect is believed to underlie a peak in risk-taking behavior and to be related to the emergence of mood and substance use disorders during adolescence (Chambers, Taylor, & Potenza, 2003; Paus, Keshavan, & Giedd, 2008; Pfeifer et al., 2011; Substance Abuse and Mental Health Services Administration, 2009). Studies have revealed important insights regarding affective development (Crone & Dahl, 2012; Guyer et al., 2016; Pfeifer & Blakemore, 2012; Pfeifer et al., 2011) and cognitive development (Dwyer et al., 2014; Larsen, Verstynen, Yeh, & Luna, 2017; Marek, Hwang, Foran, Hallquist, & Luna, 2015; Murty, Calabro, & Luna, 2016; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011; Paulsen, Hallquist, Geier, & Luna, 2015; Satterthwaite et al., 2013) that underscore the potential importance of their interaction during adolescence. By examining emotional regulation processes in detail, researchers have begun to integrate how these systems can operate in conjunction -- specifically, how the available systems of cognitive control can influence effects of emotion on behavior (Arnsten & Rubia, 2012; Hare et al., 2008; Inzlicht, Bartholow, & Hirsh, 2015; Yuan et al., 2012). However, research is still limited on the neural basis of the influence of emotion on cognitive processing during the adolescent years, which we address in the present study. Understanding neurodevelopmental changes in the neurobiology underlying the influence of emotion on cognitive control could clarify the influence of known emotional reactivity on poor decision-making and dangerous reactive behaviors in adolescence (Kann, 2016; Morris, Squeglia, Jacobus, & Silk,

2018). Thus, the present study aims to examine differences in the influence of emotional context on cognitive control from adolescence to adulthood. Based on evidence indicating heightened emotional sensitivity in adolescence (Casey et al., 2010; Guyer et al., 2016; McLaughlin, Garrad, & Somerville, 2015; Rosen et al., 2018; Steinberg, 2008) and immature cognitive control (Bjorklund & Harnishfeger, 1995; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Dempster, 1992; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Velanova, Wheeler, & Luna, 2009), we hypothesize that during adolescence, emotional states will undermine cognitive control to a greater degree than in adulthood.

Brain systems underlying adolescent emotional and cognitive processes follow unique developmental trajectories during this time (Luna & Wright, 2016; Shulman et al., 2016). Developmental models that stress the relative predominance of affective systems over executive control have been proposed for understanding the adolescent period. Dual system models focus on the effects of heightened sensitivity to reward motivation during adolescence undermining executive control leading to sensation seeking and risk-taking (Shulman et al., 2016), which may be similar regarding control of emotion during adolescence. More relevant to the current project though is the triadic model, which directly incorporates the role of emotion processing during development (Ernst, Pine, & Hardin, 2006). The triadic model proposes that motivated behavior results from the relative balance of the engagement of three major systems and their corresponding major brain regions: the reward/approach system (nucleus accumbens), the emotion/avoidance system (amygdala), and the regulation/control system (PFC) (Ernst et al., 2006). Within this framework, adolescent risk-taking leading to poor decision-making is the result of a hyperactive reward/approach system predominating over suboptimal harm/avoidance and regulatory systems. Emotional intensity and lability is a key aspect of adolescent behavior addressed by the triadic

model, which implicates poor ability of the regulatory system to exert control over the emotion/avoidance system (Ernst, 2014). However, the neurobiological basis of these interactions between the regulatory and emotion/avoidance systems is still poorly understood, motivating the present study. Our study focuses particularly on the potential for increased influence of the emotional systems on cognitive control during the transition to adulthood.

Increasing evidence informs our current understanding of the development of both emotion processing systems and the development of cognitive control independently (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; Guyer et al., 2016; Luna, 2009; Luna et al., 2015; Pfeifer et al., 2011). Notably, emotion regulation, which engages cognitive systems to respond to emotional experiences, is also maturing through adolescence (Ahmed, Bittencourt-Hewitt, & Sebastian, 2015; Casey, Heller, Gee, & Cohen, 2017; Pitskel, Bolling, Kaiser, Crowley, & Pelphrey, 2011). Studies show that the ability to regulate emotion improves with age during the transition from adolescence to adulthood, but that adolescent regulatory abilities are undermined by contextual factors such as social situations (McRae et al., 2012; Silvers et al., 2012; Tottenham, Hare, & Casey, 2011). Together, these findings indicate important changes to the emotional and cognitive systems during adolescence that position this period of development within a particularly vulnerable state of affective predominance over behavior.

Initial studies have provided crucial information delineating greater adolescent brain reactivity to individual emotional stimuli in fMRI task data (Hare et al., 2008; Rosen et al., 2018; Silvers et al., 2012). Relatively less is known about developmental changes through adolescence in how emotional *state* affects cognitive control, which is more ecologically valid in relation to real life events. Inhibitory control is a core process of cognitive control that is still undergoing maturation in adolescence, particularly regarding systems that monitor performance and ensure

proper suppression of goal incompatible responses (Luna et al., 2015). Emotional states could further undermine adolescent limitations in utilizing inhibitory control effectively, resulting in reactive and dangerous behaviors. Importantly, many of the psychiatric disorders that emerge during adolescence have prominent affective and cognitive components. For example, Major Depressive Disorder (MDD), which increases in prevalence across adolescence (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015; Costello, Copeland, & Angold, 2011), involves depressed mood or anhedonia as well as deficits in cognitive processes such as memory and executive functioning (Rock, Roiser, Riedel, & Blackwell, 2014). Studies seeking to examine the simultaneous engagement of emotional and cognitive processes during normative adolescent development may help elucidate how dysfunction in the integration of these systems could lead to the onset of psychiatric illness.

In this task and resting state functional magnetic resonance imaging (fMRI) data, we use an affective inhibitory control task performed by adolescents and adults between 14 and 31 years of age to probe the developmental effects of emotional state interacting with the inhibitory aspect of cognitive control. The study had three major aims:

*Aim 1: Characterize age-related changes in the influence of emotion on inhibitory control from adolescence to adulthood.* Behavioral measures (rate of correct responses, latency) from an affective inhibitory control fMRI task and corresponding arousal and valence ratings of the emotional stimuli were examined to assess changes across adolescent development in emotion perception and the effects of positive, negative, and neutral emotional conditions on cognitive performance.

Hypothesis: In comparison to adults, adolescents will exhibit longer latencies and a greater number of inhibitory errors in the negative condition due to the ineffectiveness of the

emotion/avoidance system (Ernst et al., 2006) but will perform closer to adult levels in the positive condition, similar to performance in reward tasks (Geier & Luna, 2009; Geier et al., 2010). Additionally, adolescents will perceive high arousal stimuli to be more arousing than adults, but valence will be perceived similarly across the age range.

*Aim 2: Characterize age-related changes in the degree of activity of relevant emotional and cognitive brain regions during performance of an affective inhibitory task.* We examined age-related changes in fMRI blood-oxygen-level-dependent (BOLD) activation of relevant brain regions during correct trials on the affective inhibitory control task and their interaction with behavior.

Hypothesis: Adolescents, compared to adults, will demonstrate increased BOLD activation compared to adults in executive regions such as the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC), due to the increased effort required to produce a correct response during competing emotional processing. Adolescents will also show greater BOLD activation in the amygdala during the negative condition and greater BOLD activation in the ventral striatum (VS) during the positive condition, based on past work showing greater amygdala response to negative affect (Guyer et al., 2008; Killgore & Yurgelun-Todd, 2007b) and greater striatal response to positive affect in the adolescent period (Braams, van Duijvenvoorde, Peper, & Crone, 2015; Galvan et al., 2006; Geier et al., 2010).

*Aim 3: Characterize age-related differences in amygdala functional brain connectivity during an emotional state.* Task-removed background connectivity, assessing emotional state, was compared to non-emotional resting state connectivity to characterize age-related differences in amygdala connectivity with the rest of the brain.

Hypothesis: Resting state amygdala connectivity will not change during the transition from later adolescence to adulthood (Jalbrzikowski et al., 2017), but amygdala background connectivity will be increased in adolescence during emotional state similar to findings in motivational state (Murty et al., 2018).

## **2.0 BACKGROUND**

### **2.1 Adolescent Development**

Adolescence depicts the period between the onset of puberty and the time when the individual gains independence and stability within society, roughly spanning the second decade of life (Blakemore & Robbins, 2012). Behaviorally, adolescence is characterized by heightened sensitivity to emotional experiences, particularly negative emotions and experiences in social contexts, which may be related to overactivity in the affective system during adolescence (Pfeifer & Blakemore, 2012). At the same time, while adult-like executive function is available by adolescence, its implementation is variable and unreliable, undermining overall performance (Luna, 2009; Luna et al., 2015; Montez, Calabro, & Luna, 2017; Ordaz, Foran, Velanova, & Luna, 2013; Ordaz, Stephanie, & Luna, 2010). This combination of heightened activity in emotional systems and continued development of the cognitive systems may limit the ability to readily engage in goal-directed behaviors and may instead lead to reactive, goal-incompatible responses including law-breaking and other potentially harmful behaviors. This dynamic of increased emotional influence over cognitive control can incur a heightened vulnerability to the emergence of mood and anxiety disorders as the brain establishes adult modes of operation.



## 2.2 Adolescent Development of Inhibitory Control

The ability to exert inhibitory control in favor of a goal-directed action is central to executive function (Bari & Robbins, 2013; Luna, 2009; Luna et al., 2004). While inhibitory control is evident in infancy (Johnson, 1995), there are significant improvements in performance into young adulthood (Bjorklund & Harnishfeger, 1995; Dempster, 1992; Geier & Luna, 2009; Luna et al., 2004; Montez et al., 2017; Ordaz et al., 2013). This protracted developmental trajectory partly stems from the brain's capacity to engage the prefrontal cortex (PFC). By mid-to-late adolescence, prefrontal activation during cognitive control is at adult levels (Ordaz et al., 2013; Simmonds, Hallquist, Asato, & Luna, 2014); however, this activation can also be unreliable and dependent on contextual factors (Adleman et al., 2002; Luna et al., 2015; Montez et al., 2017; Murty et al., 2016).

Results from fMRI studies have been less conclusive than behavioral findings, with studies reporting both age-related increases and decreases in the recruitment of prefrontal brain regions during inhibitory control tasks (Luna et al., 2001; Marsh et al., 2006; Rubia et al., 2006; Tamm, Menon, & Reiss, 2002). However, recent findings, including those from longitudinal studies, show that the prefrontal cortex is similarly engaged in adolescence and adulthood, indicating that the ability to produce an executive response is available by adolescence but that systems specific to inhibitory control, such as the dorsal ACC (dACC) are not yet functioning at adult levels (Alahyane, Brien, Coe, Stroman, & Munoz, 2014; Dwyer et al., 2014; Ordaz et al., 2013; Velanova, Wheeler, & Luna, 2008a). Thus, limitations in inhibitory control in adolescence may not be due to later development of the prefrontal cortex, but rather, may be the result of still maturing network integration relative to adults, leading to less reliable inhibitory behavior (Luna et al., 2015).

In addition to the dACC's role in performance monitoring (Botvinick & Braver, 2015), it possesses widespread connections to brain regions such as the amygdala, hypothalamus, VS, orbitofrontal cortex (OFC), and lateral prefrontal cortex, making it a key hub that supports the integration of emotion and cognitive processing (Stevens et al., 2011). Indeed, one longitudinal study found dACC activity during inhibitory control increased with age through adolescence, and this increased activity was significantly associated with decreased rates of inhibitory errors (controlling for age), indicating a clear link between the dACC and error monitoring ability (Ordaz et al., 2013). In addition, activity in the dACC mediated the association between age and inhibitory control, indicating its key role in developmental improvements.

### **2.3 Development of Emotion Reactivity, Perception, and Regulation During Adolescence**

Along with systems underlying cognitive control, the brain's affective systems also undergo significant development and specialization during adolescence. Behavioral studies have shown support for the stereotype of adolescents as overly emotional, finding that adolescents tend to be more emotionally reactive to events in their daily lives than adults and that those emotions tend to be more strongly positive or negative than those of adults (Larson, Csikszentmihalyi, & Graef, 1980). A similar study also reported that adolescents tend to have a lower baseline mood than children and report fewer extreme positive moods than children (Larson & Lampman-Petratis, 1989). These findings fit within a driven dual systems model of an overactive affective system predominating over cognitive control. However, it is important to note that this heightened emotionality is not necessarily universal to all adolescents. Rather, adolescence may be a time of

increased risk for this emotional turmoil, as opposed to a period in which emotional troubles are inevitable (Guyer et al., 2016; Hollenstein & Lougheed, 2013).

Research on the neural correlates of emotion perception in adolescents has largely consisted of tasks involving facial emotions, many of which show increased activation for emotional faces across various brain regions during the adolescent period. Specifically, the amygdala (Guyer et al., 2008; Killgore & Yurgelun-Todd, 2007a), ACC, and OFC (Monk et al., 2003) all exhibit increased activity in adolescents compared to adults during the conscious or unconscious perception of emotional facial expressions. Developmentally, one study examining the transition from childhood to early adolescence using a passive facial emotion viewing paradigm, identified increasing activity in the VS and ventromedial PFC from age 10 to 13 (Pfeifer et al., 2011). In a study examining emotional pictures, rather than faces specifically, amygdala and hippocampus activity for both positive and negative emotion was increased in adolescence, decreasing into adulthood (Vink, Derks, Hoogendam, Hillegers, & Kahn, 2014). Overall, this literature consistently demonstrates increased neural activity in limbic and affective control regions during adolescence, compared to both childhood and adulthood.

Similarly, emotion regulation, or the process of monitoring, evaluating and altering emotional experiences to accomplish goals (Thompson, 1994), is still developing during the course of adolescence, supported by other large-scale changes taking place in the brain. The ongoing development of executive functioning and other cognitive processes plays a major role in the improvements seen in emotion regulation during this period (Ahmed et al., 2015). Indeed, one study in adults found that specific aspects of executive function, such as verbal fluency, are associated with these regulatory abilities such that greater verbal fluency relates to greater ability to regulate emotion (Gyurak, Goodkind, Kramer, Miller, & Levenson, 2012). This finding was

corroborated in adolescents, with greater use of adaptive emotion regulation skills showing an association with better overall executive functioning (Lantrip, Isquith, Koven, Welsh, & Roth, 2016). Because of this relationship, the development of emotion regulation relies not only on the affective brain regions discussed in the previous chapter, but also depends on the development of cognitive regions such as the DLPFC and ACC (Ahmed et al., 2015).

Emotion regulation is often categorized into implicit and explicit forms. Implicit emotion regulation, such as the regulatory control needed for the task used in this study, occurs without conscious effort or intention to modify emotional experience. These regulatory processes are automatically engaged by the brain so that the competing task (i.e., inhibitory control) can be completed effectively. While emotion regulation research has examined the effectiveness of explicitly controlling emotion using cognitive systems, there is a paucity in the understanding of developmental changes in the neural basis of the effects of emotion on cognitive control.

## **2.4 Interactions Between Emotion and Inhibitory Control**

### **2.4.1 Negative Emotion**

Many cognitive control studies in *adults* have shown that cognitive control abilities are altered in the presence of emotional stimuli. For negative emotional stimuli in particular, studies trying to understand the nature of these alterations have shown mixed results. In some response inhibition tasks, such as go-no go and antisaccade paradigms, negative emotionally arousing task-relevant and task-irrelevant stimuli have been shown to lengthen reaction times and lower the ability to effectively inhibit a response (Albert, López-Martín, & Carretié, 2009; Mueller, 2011;

Patterson et al., 2016). In these cases, emotional stimuli may undermine the ability to effectively engage executive systems, leading to impairments in performance. However, other studies using similar tasks have shown enhanced performance in the presence of negative stimuli, such as quicker response times for threat compared to positive stimuli (Chen, Clarke, Watson, MacLeod, & Guastella, 2014) and improved response times for fearful faces compared to angry, sad, happy, or neutral expressions (Wieser, Pauli, & Mühlberger, 2009). This literature is sparse in adolescents, but one antisaccade study of healthy and anxious adolescents found that inhibitory control response latency improved in response to threat stimuli in anxious adolescents (Hardin et al., 2009).

fMRI studies in adults using emotional go-no go tasks have found that trials in which responses were inhibited showed brain activation specific to negative emotional conditions in the amygdala, VS, OFC, subgenual cingulate cortex, DLPFC, and dorsal ACC (Goldstein et al., 2007; Schulz et al., 2014), suggesting that these brain regions play a specific role in processing negative emotional stimuli while the brain is simultaneously performing a cognitive task. Another go-no go study found greater amygdala reactivity for fearful faces than for calm faces in adolescents compared to children and adults (Hare et al., 2008). While these two studies have revealed important brain regions that may be implicated in the processing of negative emotion during cognitive control, very little is known about other brain regions that may be involved, how consistently they are activated in this context, and how this brain activation is related to inhibitory control behavior. More neuroimaging studies are needed in both adults and adolescents to better understand the extended networks involved in processing negative emotion during inhibitory control and how these neural alterations may relate to the differences seen in adolescent performance.

### 2.4.2 Positive Emotion

Examining the effect of positive emotional stimuli on inhibitory control ability involves the examination of similar emotional inhibitory control tasks and tasks with an added reward component, which entail positive emotions. Most evidence in both of these areas suggests that emotional stimuli can have beneficial effects on performance in adults, such as fewer inhibitory errors in the presence of positive compared to negative or neutral stimuli (Albert et al., 2009; Stigchel, Imants, & Richard Ridderinkhof, 2011). A study of healthy and anxious adults also showed that healthy adolescents displayed faster reaction times for positive stimuli as compared to threat stimuli (Hardin et al., 2009). Reward processing studies using incentivized antisaccade tasks have also shown that adolescent error rates can reach closer to adult levels with the addition of a reward component (Geier et al., 2010; Padmanabhan et al., 2011; Paulsen et al., 2015). This work suggests that not only can positive affect enhance inhibitory control performance, but that this enhancement is pronounced during the adolescent period.

Some neuroimaging studies have started to investigate the neural correlates of this interaction between positive emotions, specifically those associated with an incentivized task, and inhibitory control. Studies using rewarded antisaccade studies show increased activity in adolescents, compared to adults and children, in both the VS and the specialized executive circuitry needed to perform the behavior that will result in the reward (Geier et al., 2010; Padmanabhan et al., 2011). These effects are specific to different stages of rewarded inhibitory control with lower BOLD activation in adolescents in the VS compared to adults during the assessment of the reward cue (Reward vs. Neutral) but heightened VS activation during the preparation to execute a correct incentivized inhibitory response (Geier et al., 2010). In the context that adolescents show worse performance than adults in non-rewarded antisaccade tasks, (Ordaz et al., 2013), these results

suggest that increased engagement of reward processing in adolescence may drive the immature executive system to exert itself in order to obtain the reward. In addition, adults were found to engage the OFC to a greater extent than children or adolescents during reward trials (Padmanabhan et al., 2011). This implies that, as suggested by the triadic model (Ernst et al., 2006), adolescent behavior is more dominated by reward-associated brain regions (such as the VS) while adults are better able to recruit prefrontal areas to regulate the influence of the reward and emotion regions.

Together, these past studies confirm that there is unique influence of emotion affecting cognitive control task performance. Positive affect appears to improve performance across studies, however, the influence of negative affect is less consistent in the current literature. One unique study in adults showed that the influence of emotion on antisaccade performance may be modulated by the level of cognitive load, such that emotional stimuli significantly affects cognitive performance under low load (performing an antisaccade task) but has no effect when the cognitive load is high (simultaneously performing a memory task) (Berggren, Richards, Taylor, & Derakshan, 2013). If the effects of emotion on inhibitory control depend heavily on cognitive load, it is possible that inconsistency of tasks and testing conditions across studies could account for the many conflicting findings in this area of research.

To augment the few studies on adolescents mentioned above, Aim 1 of the current study will provide additional input on the behavioral effects of emotion on inhibitory control in adolescence as compared to adulthood. However, the literature on the neural correlates of interactions between positive/negative emotion and cognitive control is minimal in adults and virtually nonexistent in adolescents. Thus, the current study will begin to address a substantial gap in the current understanding of emotional influences in inhibitory control through development. Aim 2 will probe associations in task-based brain activity with a focus on adolescence and

importantly, Aim 3 will explore how an emotional *state* affects underlying brain connectivity, integrating emotional processing to provide novel insight into the nature of the effects of emotion on behavior.

## **2.5 Background Connectivity**

As mentioned in the previous section, the current literature includes very few studies examining emotion-cognition interactions in adolescence. While the first two aims of this study will directly assess age-related changes in the effects of emotion on the behavioral and neural underpinnings of inhibitory control averaged across trials, sustained emotional states operating beyond task-related effects may have unique influence on inhibitory control (Harlé, Shenoy, & Paulus, 2013). Context can establish a response state that informs effects of emotion beyond the trial level, and thus may be more consistent with real life situations. Thus, the third aim will explore effects of emotional state on brain activation during inhibitory control using a more recent method known as background connectivity (Al-Aidroos, Said, & Turk-Browne, 2012; Ganger et al., 2015; Norman-Haignere, McCarthy, Chun, & Turk-Browne, 2012). This technique assumes that task-evoked signals and spontaneous background fluctuations are linearly superimposed in task-based fMRI data. As such, the removal of task-based signals should leave behind the sustained state-related activity that is modulated by the context of the task (Al-Aidroos et al., 2012; Murty et al., 2018). Because prior evidence suggests that adolescents experience more extreme emotional states than adults and more negative emotional states than children (Larson et al., 1980; Larson & Lampman-Petratis, 1989), and some research indicates that negative emotion may impair cognitive control abilities (Albert et al., 2009; Hare et al., 2008; Mueller, 2011; Patterson et al.,



2016), background connectivity could reveal how amygdala functioning may be altered in emotional contexts.

## **2.6 The Current Study**

In this study, we examined age-related changes from adolescence to adulthood in behavior and brain processing during an emotional inhibitory control task. Specifically, using a cross-sectional dataset comprised of 50 participants ranging from 14 to 31 years old, we tested for age-related changes in the effects of task-irrelevant emotional stimulus processing on inhibitory control performance, task-related activation, and amygdala background connectivity. In this manner, we can assess the influence of emotional state on adolescent abilities to inhibit unwanted behaviors and the neural correlates of these effects. We anticipated greater effects of emotion on inhibitory control in adolescence, which decrease into adulthood. Task activation analyses are expected to uncover age-related changes in cognitive control regions and differences by emotional condition in affective regions such as the amygdala. By incorporating an analysis of amygdala background connectivity, we will be able to conduct a data-driven exploration of age-related changes in amygdala connectivity specific to an emotional context relative to its connectivity at rest, providing insight into the effects of heightened adolescent emotionality on the brain.

## **3.0 METHODS**

### **3.1 Participants**

Neuroimaging (task and resting state) and behavioral data were collected on 66 participants (14–31 years old) as part of a multimodal cross-sectional study. Participants did not have a psychiatric disorder determined by a phone screen and a clinical questionnaire (Achenbach & Rescorla, 2001, 2003). Participants were native English speakers reporting no history of neurological problems. Task data were available for 50 participants (25 female subjects, Figure 1) and resting state data were available for 49 participants (25 female subjects, Figure 2) with exclusions based on excessive motion (task N=2, rest N=7) and missing data files (task N= 12, rest N=8). Two additional subjects were excluded from both datasets due to psychiatric diagnoses disclosed after data collection.

### **3.2 fMRI Task Design**

During fMRI scanning, participants completed a standard antisaccade task (Hwang, Velanova, & Luna, 2010; Ordaz et al., 2013; Velanova et al., 2008, 2009) with an added affective element (Figure 3). Each antisaccade trial began with a red fixation cross displayed on a projector screen within the scanner for 3 seconds. Next, a red “x” lasting 1.3 seconds appeared, followed quickly (black screen for 0.2 seconds) by a yellow dot (the “cue”) in an unpredictable location along the horizontal meridian of the screen, at which point participants had been previously

instructed to look at the mirror location on the opposite side of the screen. The cue would remain on the screen for 1.5 seconds and would be immediately followed by another red fixation cross during a variable inter-trial interval lasting between 2 and 10 seconds before the start of the next trial. Participants completed four consecutive runs of this task, with 28 trials in each run (total trials: 112).

The affective element consisted of a six-second positive, negative, or neutral sound. Examples of sounds chosen for this task within each category appear in the table below (Figure 4). The sound began three seconds before the start of each antisaccade trial, when the red fixation cross first appeared and ended when the yellow cue disappeared from the screen. Sounds were taken from the International Affective Digitized Sounds (IADS), a set of sounds that has been tested across genders in healthy college-age adults for consistency in perception of valence and arousal (Bradley & Lang, 2000). From the full database, sounds that were inappropriate for children (i.e. “erotic” sounds) and those that were inconsistent over the 6 second period or difficult to identify were not considered for inclusion in the task. Thus, 28 sounds were chosen for each run based on their average valence and arousal ratings provided in the IADS database (Bradley & Lang, 2007). Arousal ratings were given on a scale of 1 (lowest arousal) to 9 (highest arousal). Similarly, the valence scale also spanned the 1 to 9 range, with 1 representing sounds that produced strong feelings of unhappiness and a 9 representing sounds producing very happy feelings (Figure 5). In the reference group, positive sounds had a positive valence rating (7-9) and a high arousal rating (7-9), while negative sounds also had a high arousal rating but a negative valence rating (1-3). Neutral sounds had a medium valence rating (4-6) and a low arousal rating (1-3). An equal number of trials were also included in which no sound played before the corresponding antisaccade

trial (the control condition). Each run of the task included 7 runs of each type (positive, negative, neutral, or control) for a total of 28 trials per condition.

### **3.3 MR Data Acquisition**

Data were acquired using a Siemens 3T Magnetom Trio scanner (Siemens Medical Solutions, Erlangen, Germany) at the University of Pittsburgh Medical Center Magnetic Resonance Research Center using a 12-channel phased-array head coil. Functional images were acquired using an echo-planar sequence sensitive to blood oxygen level-dependent contrast (T2\*). Four runs of task-based fMRI data were collected (each run: three minutes, two seconds). The fMRI scan parameters for the task were the following: repetition time (TR)/echo time = 2000 ms/20 ms, flip angle = 80°, voxel size = 1.71875×1.71875 mm in plane, 33 3-mm axial slices separated by gaps of 0.75 mm, 728 TRs. We collected five minutes of resting-state data with eyes closed while awake. rsfMRI parameters were the following: repetition time (TR)/echo time = 2000 ms/20 ms, flip angle = 80°, voxel size = 1.719×1.719 mm in plane, 33 contiguous 3.75-mm axial slices, 150 TRs. A magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence was acquired to measure brain structure and for alignment of the fMRI images. Magnetization prepared rapid acquisition gradient-echo sequence parameters were the following: TR/echo time = 2100 ms/3.43 ms, flip angle = 8°, inversion time = 1050 ms, voxel size = 1×1 mm, 192 contiguous 1-mm slices.

### **3.4 Eye Tracking Data Acquisition**

Eye-tracking data were collected using a long-range optics eye-tracking system from Applied Science Laboratories (Model 504LRO; Bedford, MA). Eye-position was obtained via pupil-corneal reflection observed in the reflection of a head coil-mounted mirror with  $0.5^\circ$  of visual angle. Video monitoring was also used to ensure compliance. A 9-point calibration was performed prior to the experimental session and between runs when necessary. Stimuli were presented using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) and projected onto a flat screen behind the scanner, visible to the subject through the coil-mounted mirror. Eye data were scored off-line using ILAB and MATLAB software (MathWorks, Inc.).

### **3.5 Eye Tracking Data Scoring**

Correct responses in the antisaccade task were defined as those in which the first eye movement during the saccade epoch with velocity greater than or equal to  $30^\circ/\text{sec}$  was made toward the mirror location of the peripheral cue and extended beyond a  $2.5^\circ$  visual angle from central fixation. Incorrect responses occurred when the first saccade during the saccade epoch was directed toward the peripheral stimulus and exceeded the  $2.5^\circ$  visual angle central fixation zone but were subsequently directed to the correct location, indicating that the instructions were being followed. Trials in which no eye movements were generated, or in which the tracker lost fixation, were excluded from analyses.

### 3.6 fMRI Preprocessing

Both task and resting state fMRI data were preprocessed using a preprocessing pipeline that incorporates tools from AFNI, NiPy, and Freesurfer. The first 4 TRs from all scans were removed to allow for BOLD signal normalization. Functional images were warped into MNI standard space using a series of affine and nonlinear transforms. Normalization based on global mode was then calculated on the functional images. Next, all functional images were spatially smoothed using a 6-mm full width at half maximum Gaussian kernel. Removal of non-stationary events in the fMRI time series was conducted using wavelet despiking (Patel & Bullmore, 2016). For the resting state scans, we then conducted simultaneous multiple regression of nuisance variables and bandpass filtering at  $0.009 \text{ Hz} < f < 0.08 \text{ Hz}$  to better control nuisance-related variability (Hallquist, Hwang, & Luna, 2013). Nuisance regressors included were non-brain tissue (NBT), average white matter signal, average ventricular signal, six head realignment parameters obtained by rigid body head motion correction, and the first derivatives of these measures. NBT, average white matter, and average ventricular signal nuisance regressors were created using Freesurfer's automated segmentation program and extracted from each participant's MPRAGE scan (Fischl et al., 2002). We then removed any remaining high motion volumes via scrubbing procedure in both task and resting state scans. For all subjects, we calculated two quality control measures with respect to head motion: volume-to-volume frame displacement, (FD) and the RMS derivative of fMRI time series (DVARs). Similar to previous publications from our group (Marek et al., 2015), we censored and removed volumes that had an  $FD > 0.5 \text{ mm}$  and/or  $DVARs > 5$  (computed after wavelet despiking), as well as the frame preceding the motion artifacts and the two subsequent frames. By first implementing wavelet despiking, we can use most of the time series data to provide a more reliable estimate of the true correlation between two regions-of-

interest (ROIs) (Patel & Bullmore, 2016). However, because motion is such a critical issue in developmental studies and there were some remaining DVARS values over the identified threshold after wavelet despiking, these volumes were censored as extra validation to ensure that motion was not contaminating the signal. Subjects were dropped from each fMRI analysis if more than 15% of their volumes were removed via this censoring process. Resting state analyses shown in the results did not incorporate global signal regression; however, the same analyses were carried out with global signal regression and no notable differences in connectivity results were found.

### **3.7 Data Analysis**

#### **3.7.1 Aim One**

*Aim One: Characterize age-related changes in the influence of emotion on inhibitory control from adolescence to adulthood.*

Behavioral data were analyzed with a linear mixed-effects regression using the lme4 package in R (R Development Core Team, Vienna, Austria) (Bates, Mächler, Bolker, & Walker, 2014). A linear-mixed effects model was used to examine the fixed effects of condition, age, sex, and their interactions on the four dependent variables: error rate (inhibitory failures), response latency, arousal ratings, and valence ratings. Subject was included in the model as a random effect. Within this model, linear, inverse, and quadratic forms of age were examined and Akaike's Information Criterion (AIC), a commonly used measure for model selection (Akaike, 1974), was used to determine the model with the best fit (i.e., the lowest AIC). Significant main effects or

interactions were further disambiguated by performing post hoc analyses using the R package ‘lsmeans’.

### **3.7.2 Aim Two**

*Aim Two: Characterize age-related changes in the degree of activity of relevant emotional and cognitive brain regions during performance of an affective inhibitory task.*

#### **3.7.2.1 First Level Analysis**

To obtain task activation, subject data were processed using the 3dDeconvolve tool from the Analysis of Functional NeuroImages (AFNI) software, which uses multiple linear regression to estimate the average hemodynamic response at each voxel given an input time series (Cox, 1996). This deconvolution model included five regressors of interest: 1) correct trials with positive sounds, 2) correct trials with negative sounds, 3) correct trials with neutral sounds, 4) correct trials with no sounds, and 5) all error and dropped trials, convolved using a TENT function. In addition, 16 regressors of no interest were modeled: 6 rigid body head motion parameters, average ventricular signal, average white matter signal, and the first derivatives of these measures.

#### **3.7.2.2 Second Level Analysis**

The AFNI command 3dMVM was used to examine voxelwise developmental effects across the whole brain. 3dMVM is a group analysis program in AFNI that performs ANOVA-style computations and multiple linear regression using multivariate modeling (Chen, Saad, Adleman, Leibenluft, & Cox, 2015). 3dMVM was used to test for the main effects of age, condition, TR and their interactions across the whole brain in a multiple linear regression. Age and sex were included



as between-subjects variables, while condition and TR were set as within-subjects variables. Results were corrected for multiple comparisons using a combination of cluster size and voxel probability, with parameters determined through a Monte Carlo simulation using AFNI's 3dClustSim program on randomly generated data within the task-related activation mask with the same smoothness as the group mean smoothness estimated from first-level residuals for each region. This analysis specified the cluster size threshold applied with a single voxel threshold of  $p < .005$  that was required to achieve a cluster-wise corrected  $p < 0.05$ . This implementation is the most current, stringent procedure recommended by the AFNI developers to prevent against obtaining false positive clusters of connectivity (G. Chen et al., 2015). Significant clusters with main effects of age, condition or interactions was identified. Mean parameter estimates were extracted for these clusters with 3dROIStats and follow-up post hoc tests were performed.

### **3.7.3 Aim Three**

*Aim Three: Characterize age-related differences in amygdala functional brain connectivity during an emotional state.*

#### **3.7.3.1 First Level Analysis**

Background connectivity was obtained by using the residuals obtained from the deconvolution model described above (First Level Analysis, Aim 2), which provided an estimate of the data after eliminating the effects of task stimuli on the hemodynamic response. Because these data resemble resting state fMRI data, the residuals were bandpass filtered ( $0.009 \text{ Hz} < f <$

0.08 Hz) to allow for comparison with the resting state dataset and eliminate extreme values in the estimated hemodynamic response (Geerligs, Rubinov, Cam-CAN, & Henson, 2015).

Left and right amygdala ROIs were obtained from the Harvard-Oxford Subcortical Atlas, distributed with FSL (<http://www.fmrib.ox.ac.uk/fsl/>), and a bilateral amygdala ROI was created by combining these two ROIs using the 3dCalc tool in AFNI. For both the resting state data and residuals from the task, mean time courses for the amygdala ROI were created for each individual using AFNI's 3dROIstats. Voxelwise regressions were performed on the preprocessed data using AFNI's 3dDeconvolve to compare the average amygdala ROI time series with each timeseries for all other voxels in the brain. These analyses resulted in voxelwise subject-level maps of Pearson correlations ( $r$ ) between the average amygdala ROI time course and each voxel's time course. For all statistical analyses,  $r$ -values were first normalized using the Fisher  $r$ -to- $z$  transformation.

### **3.7.3.2 Second Level Analysis**

3dMVM was used again to test for the voxelwise effects of age and sex on amygdala background connectivity in a multiple linear regression. This analysis was masked to only consider voxels with a 50% or greater probability of being grey matter in the MNI-152 template. Significant clusters with main effects of age were identified and mean parameter estimates were subsequently extracted for these clusters with 3dROIstats, followed by post hoc testing to determine the nature of these age effects. Results were corrected for multiple comparisons using the cluster correction method described above (Second Level Analysis, Aim 2).

## 4.0 RESULTS

### 4.1 Aim One

*Aim One: Characterize age-related changes in the influence of emotion on inhibitory control from adolescence to adulthood.*

Models examining the fixed effect of age alone on each behavioral outcome (arousal rating, valence rating, percentage of correct response, latency) were first tested to determine which form of age (linear, quadratic, inverse) produced the best model fit, based on AIC values. Because the AIC values of these three models never differed by more than 2 points, there was no strong evidence for preferring one model over another. Thus, the mathematically simplest model, linear age, was used throughout these analyses. For consistency and ease of comparison between behavioral and imaging results, linear age was also used throughout the neuroimaging analyses.

#### 4.1.1 Percentage of Correct Responses

A linear mixed-effects model was used to examine the effects of age, emotional condition, and their interaction on percentage of correct responses (Figure 6). Gender was included as a covariate and subject was included as a random effect. There was a significant effect of condition ( $\chi^2=9.2507$ ,  $p=0.02614$ ) and trending fixed effects of age ( $\chi^2=3.6321$ ,  $p=0.05668$ ) and gender ( $\chi^2=3.6080$ ,  $p=0.05750$ ). There was no significant age-by-condition interaction effect, however, the effect of age did reach significance within the negative condition only, such that increasing age

was associated with a greater percentage of correct responses ( $p=0.0270$ ). The age effect did not reach significance within the positive, neutral, or silent conditions.

#### **4.1.2 Response Latency**

Another linear mixed-effects model measured the fixed effects of age, emotional condition, and their interaction on response latency of correct trials (in milliseconds), with gender as a covariate and subject as a random effect (Figure 6). There were no significant effects of age, condition, or sex, but there was a significant age-by-condition interaction ( $\chi^2=11.6843$ ,  $p=0.008547$ ). This was driven by a significant association between increasing age and improvement in response latency within the silent condition ( $p=0.0240$ ) and a trending age association with response latency enhancements in the positive condition ( $p=0.0573$ ).

#### **4.1.3 Arousal and Valence Ratings**

A mixed-effects model was used to examine the fixed effects of age and emotional condition on arousal ratings of emotional stimuli, with gender as a covariate and subject as a random effect (Figure 7). As expected, a significant effect of emotional condition was found, indicating that subjects perceived significant differences in the level of arousal elicited by stimuli from different emotional conditions. No significant sex effect was present, but a trending effect of age was observed ( $\chi^2=3.5116$ ,  $p=0.06094$ ) as well as a significant age-by-condition interaction ( $\chi^2=9.1437$ ,  $p=0.01034$ ). This was consistent with a significant age effect in the negative condition, such that increasing age was associated with higher arousal ratings ( $p=0.0087$ ).

Another mixed-effects model incorporated the fixed effects of age and emotional condition and the random effect of subject on valence ratings of emotional stimuli, with gender included as a covariate (Figure 8). Consistent with the valence-based categorization of the emotional conditions, there was a significant difference in valence ratings between emotional conditions ( $\chi^2=2295.0139$ ,  $p=2 \times 10^{-16}$ ). However, no effects of age, gender, or the interactions between age, gender, and condition were observed. In addition, no significant age effects were found within individual conditions.

## 4.2 Aim Two

*Aim Two: Characterize age-related changes in the degree of activity of relevant emotional and cognitive brain regions during performance of an affective inhibitory task.*

### 4.2.1 fMRI Task Activation

Details of significant clusters are given in Tables 1 and 2. The auditory cortex, right posterior cingulate, left DLPFC, angular gyrus, inferior temporal gyrus, and superior temporal sulcus all showed differential recruitment by emotional condition across time course ( $F=1.956$ ,  $p<0.001$ , Table 1, Figure 9). The difference between conditions in the activation of the auditory cortex bilaterally remained even when the silent condition was not included in the analysis, indicating that this variation within the auditory cortex does not simply reflect the presence or absence of sound. Notably, the main effect of emotional condition contrast (independent of change across time course) revealed similar regions of differential activation, but also included the

amygdala bilaterally ( $F=5.733$ ,  $p<0.001$ , Figure 10). This result implies that while the amygdala is not responding differentially across a trial (as might be the case if its activity was involved in task performance), but that its average overall activation differs, providing additional rationale for pursuing a background connectivity analysis. Post-hoc pairwise comparisons suggest that these differences between conditions may be attributable to significant differences between BOLD activation in the silent condition and all other conditions, as well as significantly different activation between the negative and neutral conditions in many clusters. Age-related differences across time course were evident in the visual association cortex, postcentral gyrus, medial PFC, left superior temporal gyrus, inferior frontal gyrus, and the precuneus ( $F=2.905$ ,  $p<0.001$ , Table 2, Figure 11). There were no main or interaction effects of gender, and no age-by-condition or age-by-condition-by-TR interactions in brain activation were observed at this threshold.

### **4.3 Aim Three**

*Aim Three: Characterize age-related differences in amygdala functional brain connectivity during an emotional state.*

#### **4.3.1 Background Connectivity**

Age-associated changes were observed in the background connectivity of the amygdala bilaterally to the rest of the brain (Table 3, Figures 12-13). At a voxelwise threshold of  $p<0.005$  and a cluster-corrected threshold of  $p<0.05$ , amygdala connectivity was found to increase with age in the dorsal ACC, Brodmann Area 10, precuneus, medial PFC, DLPFC, right insula, right

thalamus, and scattered areas throughout the parietal cortex ( $t=2.952$ ). In the resting state dataset, significant age-related changes in amygdala connectivity were found only in the occipital cortex ( $p<0.005$  voxelwise,  $p<0.05$  corrected). To test the specificity of these connectivity changes to the task context, the bilateral amygdala ROI and significant clusters derived from the background connectivity analyses were combined into one mask, and pairwise connectivity values were calculated for these ROIs within the resting state data. These analyses showed no significant correlations between the amygdala and the clusters, providing some evidence that this pattern of age-related change in amygdala connectivity found in the background connectivity analysis is specific to an emotional state.

## 5.0 DISCUSSION

This study probed the direct and contextual effects of emotional processing on cognitive control. Unlike most studies of emotion perception, which incorporate visual stimuli, this task included auditory affective stimuli to fully dissociate it from the visual cognitive control task. We characterized age-related differences in behavior and brain processes underlying task and emotional state on inhibitory control systems.

The perceived arousal of stimuli and percent of correct responses increased significantly with age in the negative condition only. In addition, BOLD activation differences across conditions were largely driven by significantly greater activation in the negative condition compared to the neutral and silent conditions. The fact that all of these findings are specific to the negative emotional condition is in line with many studies which suggest that effects are more prominent for negative emotional stimuli, as compared to positive or neutral stimuli (García-Pacios, Garcés, Del Río, & Maestú, 2015; Hare et al., 2008; Killgore & Yurgelun-Todd, 2007b). However, the increase in perceived arousal of negative stimuli with age could be considered novel, since adolescents are often believed to be more prone to intense emotions. While it may seem problematic to interpret the relationship between brain activation and age if these stimuli are perceived differently by different age groups, it should be noted that the valence of the stimuli were rated similarly across all ages. In other words, participants on average perceived the same stimuli to be positive, negative, or neutral. Thus, subjects are likely all differentiating the essential emotion represented by the stimuli in the same way, and the differences with arousal in age thus reflect how much that perceived emotion affects each individual.



These results suggest that adults perceive negative stimuli as more arousing but are simultaneously more capable of using that arousal to their benefit. This is in line with the arousal-biased competition theory, positing that arousal influences the “strength of competing mental representations”, which serves to improve memory encoding for those stimuli that are most goal-relevant (Mather & Sutherland, 2011). While the original theory attempts to explain a memory phenomenon, a similar idea may apply to other cognitive tasks such as inhibitory control, especially when they involve task-irrelevant arousal-inducing stimuli. Alternatively, adults may have greater understanding of their own arousal than adolescents, which may intensify known limitations in adolescent emotion regulation abilities (Guyer et al., 2016; Scheibe & Blanchard-Fields, 2009). This theory would suggest that their difficulty regulating emotion may result from low awareness of their own increasing arousal, leading to excessive reactions and a lack of behavioral control. Incorporating a measure of objective arousal, such as pupillometry data, may help to confirm this theory in a future study.

Age-related improvements (decreases) in the latency of correct inhibitory responses were only evident in the silent condition, similar to typical antisaccade studies (Bjorklund & Harnishfeger, 1995; Dempster, 1992; Luna et al., 2004). The presence of an auditory cue may thus act as a competing process that undermines cognitive control due to increasing efficiency of executive functions throughout adolescence.

The background connectivity analysis sought to understand the contextual effects of emotion on the brain, and how these effects change in the transition from adolescence to adulthood. While previous work has shown that resting state amygdala connectivity significantly decreases with age through childhood and early adolescence, these decreases occurred with specific areas of the prefrontal cortex, and greatest change was shown to occur earlier in adolescence (Jalbrzikowski

et al., 2017). Therefore, throughout the age range examined in the current study, resting state amygdala connectivity would be expected to plateau, consistent with past findings and the lack of age-related change found here. However, background connectivity, representing emotional state, showed that amygdala connectivity was greater in adulthood. These age-related increases in background connectivity are present in the context of age-related improvements in performance and increasing perceived arousal mentioned above.

The areas engaged to a greater extent by the amygdala in adulthood, as compared to adolescence, include those involved in general executive functioning, such as the DLPFC and ACC. Furthermore, the areas comprise relevant functional connectivity networks, such as the dorsal attention network and salience network. The fact that both of these networks are more engaged by the amygdala with age suggests that the amygdala is better able to communicate salience information to cortical areas which can help appropriately direct attention during the task. Additionally, because these connectivity changes are specific to the emotional state, the increased engagement of necessary attentional systems may be part of a developmental process independent of any changes in the task-relevant activation essential to completion of the cognitive control task, or changes in the intrinsic connectivity of these networks.

Taken together, our results suggest that greater awareness of emotional arousal from adolescence to adulthood may be related to increased engagement of relevant cortical areas by the amygdala in an emotional context that would support enhanced cognitive control enhancing emotion regulation. As such, age-related increases in background connectivity may reflect strengthening of top-down cortical to amygdala control into adulthood providing greater control of emotional reactivity. The greater awareness in adulthood of emotional arousal may signal the need to support greater resources increasing cortico-amygdala engagement. Future longitudinal

studies using a significantly larger sample size encompassing a wider age range will be important to better elucidate the results suggested by the present study.

## **6.0 CONCLUSION**

The current study found simultaneous age-related increases in arousal, background amygdala connectivity, and task performance during the transition from adolescence to adulthood. The results suggest that from adolescence to adulthood, greater accuracy in the appraisal of emotional arousal may lead to stronger integration of cortical and amygdala processing, enhancing behaviors that require executive control. Decreased processing of emotional arousal may undermine the capacity of adolescents to effectively engage control processes that may contribute to known poor decision-making in emotionally taxed circumstances.

## APPENDIX A TABLES

**Table 1: Clusters from Voxelwise Analysis of Task Activation - Condition x TR Contrast (p<0.001 voxelwise, p<0.05 corrected)**

Name	Brodmann Area	X	Y	Z	# of voxels
R Auditory Cortex	BA 22/41/42	-52.5	+13.5	+7.5	1197
L Auditory Cortex	BA 22/41/42	+55.5	+22.5	+10.5	947
R Dorsolateral Prefrontal Cortex	BA 46	-43.5	-22.5	+22.5	134
L Angular Gyrus	BA 39	+40.5	+82.5	+37.5	122
L Dorsolateral Prefrontal Cortex	BA 46	+43.5	-22.5	+22.5	84
R Angular Gyrus	BA 39	-52.5	+67.5	+28.5	78
L Posterior Cingulate / Precuneus	BA 31	+16.5	+58.5	+16.5	75
L Inferior Temporal Gyrus	BA 37	+49.5	+73.5	+7.5	51
R Inferior Temporal Gyrus	BA 37	-52.5	+61.5	-1.5	28
L Cerebellum	-	+16.5	+79.5	-31.5	25
R Cerebellum	-	-13.5	+76.5	-34.5	25
L Cerebellum	-	+10.5	+79.5	-40.5	23
R Dorsolateral Prefrontal Cortex	BA 8	-43.5	-7.5	+49.5	16
L Superior Temporal Sulcus	BA 39	+52.5	+67.5	+31.5	15
Posterior Parietal Cortex	BA 2	+64.5	+28.5	+40.5	15
L Fusiform Gyrus	BA 37	+55.5	+52.5	-22.5	13

**Table 2: Clusters from Voxelwise Analysis of Task Activation - Age x TR Contrast ( $p < 0.001$  voxelwise,  $p < 0.05$  corrected)**

<b>Name</b>	<b>Brodmann Area</b>	<b>X</b>	<b>Y</b>	<b>Z</b>	<b># of voxels</b>
R Occipital Cortex	BA 18	-1.5	+82.5	+16.5	75
L Lingual Gyrus	BA 19	+16.5	+55.5	-7.5	48
R Fusiform Gyrus	BA 37	-37.5	+61.5	-13.5	46
R Lingual Gyrus	BA 18/19	-16.5	+70.5	-1.5	34
Motor Cortex	BA 4	-58.5	+16.5	+28.5	27
L Superior Frontal Gyrus	BA 10	+16.5	-61.5	+31.5	24
R Parahippocampal Gyrus	BA 19/30	-22.5	+61.5	-4.5	18
R Medial Frontal Gyrus	BA 10	-4.5	-58.5	+13.5	17
R Hippocampus	-	-25.5	+43.5	-10.5	15
R Parahippocampal Gyrus	BA 30	-13.5	+37.5	-1.5	13
L Angular Gyrus	BA 39	+43.5	+73.5	+34.5	13

**Table 3: Clusters from Voxelwise Analysis of Age Effects on Amygdala Background Connectivity (p<0.005 voxelwise, p<0.05 corrected)**

Name	Brodmann Area	X	Y	Z	# of voxels
Bilateral Precuneus	BA 7	+7.5	+64.5	+46.5	693
Medial Frontal Gyrus	BA 9	+1.5	-52.5	+16.5	249
R Superior Frontal Gyrus	BA 10	-25.5	-55.5	+19.5	96
R Dorsolateral Prefrontal Cortex	BA 8	-40.5	-31.5	+46.5	82
L Medial Frontal Gyrus / Anterior Cingulate Cortex	BA 32	+4.5	-61.5	-1.5	81
R Inferior Parietal Lobule	BA 40	-46.5	+61.5	+49.5	48
R Angular Gyrus	BA 39	-43.5	+70.5	+31.5	44
L Dorsolateral Prefrontal Cortex	BA 8/9	+37.5	-28.5	+46.5	43
R Inferior Parietal Lobule	BA 40	-58.5	+58.5	+31.5	38
R Inferior Parietal Lobule	BA 40	-46.5	+43.5	+40.5	36
L Superior Frontal Gyrus	BA 10	+25.5	-58.5	+7.5	35
L Fusiform Gyrus	BA 18/19	+25.5	+76.5	-4.5	33
R Insula	BA 13	-40.5	+16.5	+16.5	28
L Middle Temporal Gyrus	BA 39	+46.5	+79.5	+22.5	24
R Thalamus	-	-10.5	+16.5	+19.5	22
L Middle Frontal Gyrus	BA 6	+1.5	+1.5	+61.5	22

## APPENDIX B FIGURES

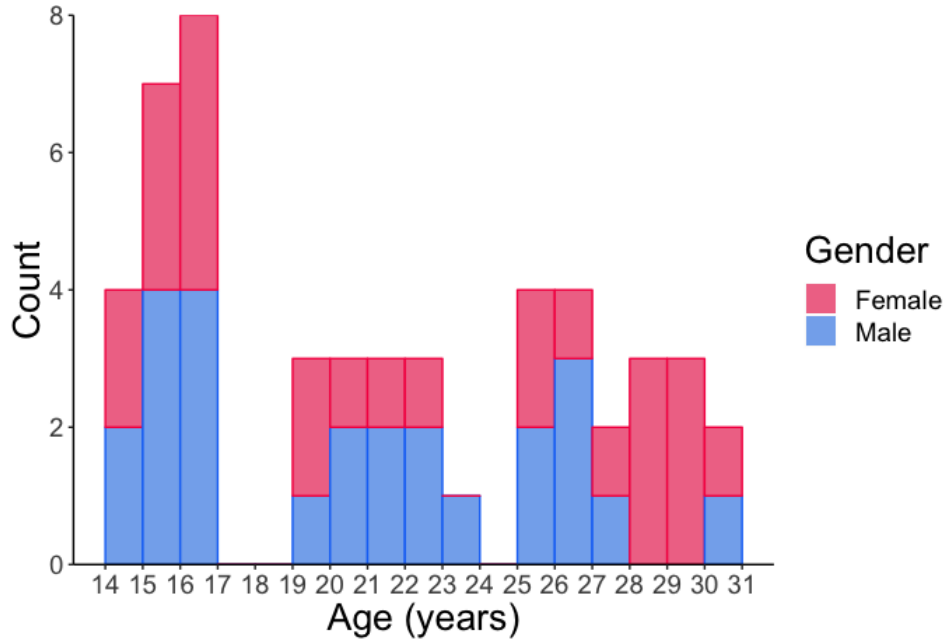


Figure 1: Histogram showing age distribution of task subject pool, grouped by gender.

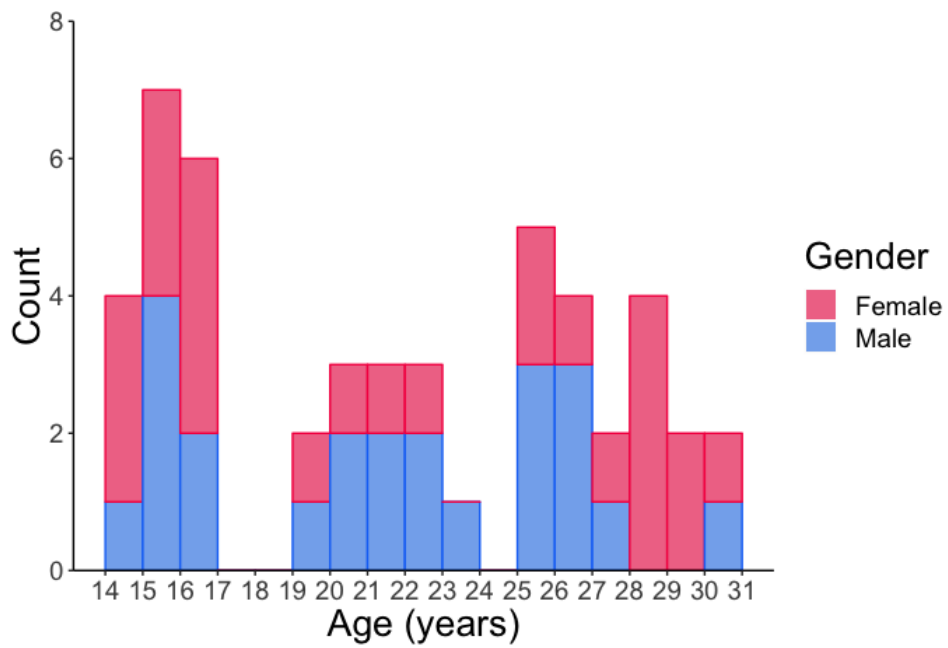


Figure 2: Histogram showing age distribution of rest subject pool, grouped by gender.



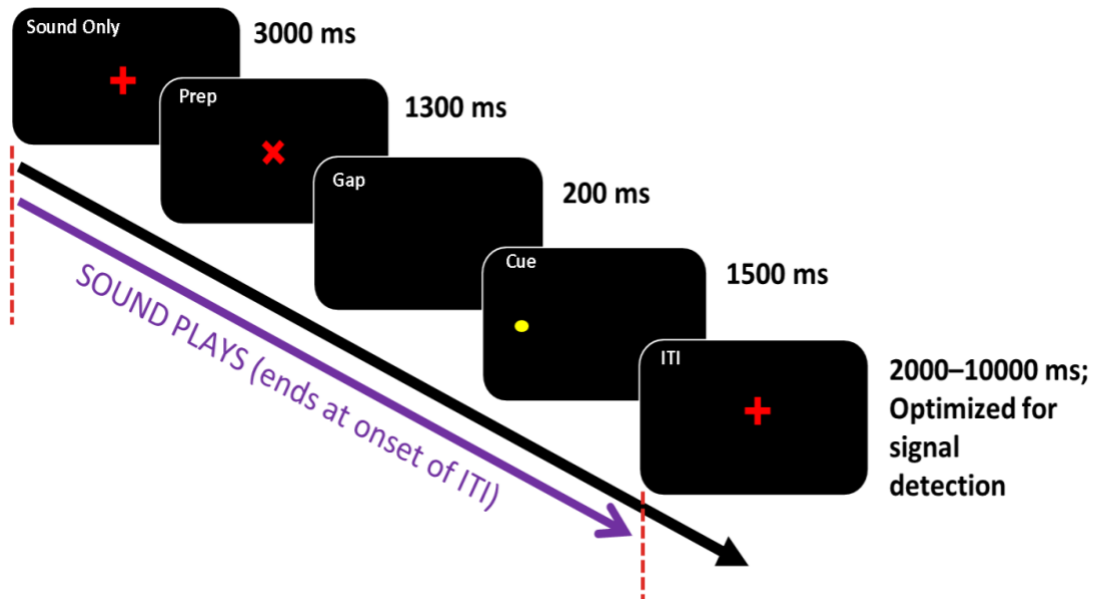
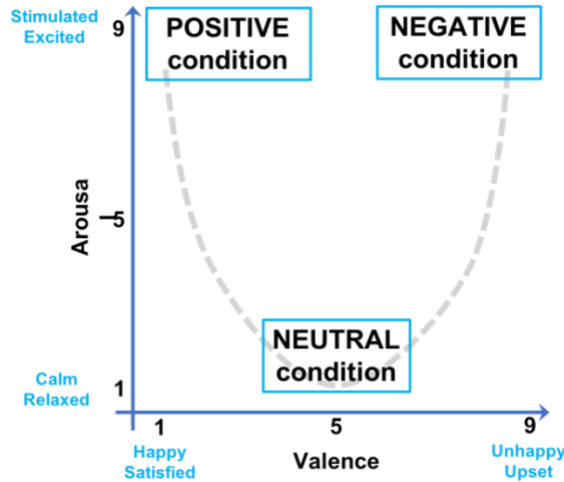


Figure 3: Diagram of affective antisaccade task design.

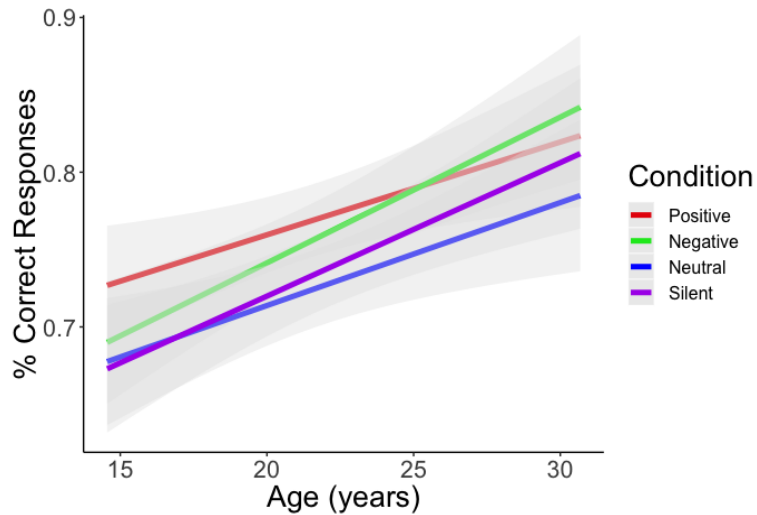
Positive	Negative	Neutral
<ul style="list-style-type: none"> <li>• Applause</li> <li>• Laughter</li> <li>• Slot machine</li> <li>• Cheering crowd</li> </ul>	<ul style="list-style-type: none"> <li>• Screaming</li> <li>• Bomb explosions</li> <li>• Sirens</li> <li>• Vomiting</li> </ul>	<ul style="list-style-type: none"> <li>• Waterfall</li> <li>• Typewriter</li> <li>• Wind blowing</li> <li>• Printer</li> </ul>

Figure 4: Examples of positive, negative, and neutral sounds included in task.



**Figure 5: Graphical representation of the arousal-by-valence relationship.**

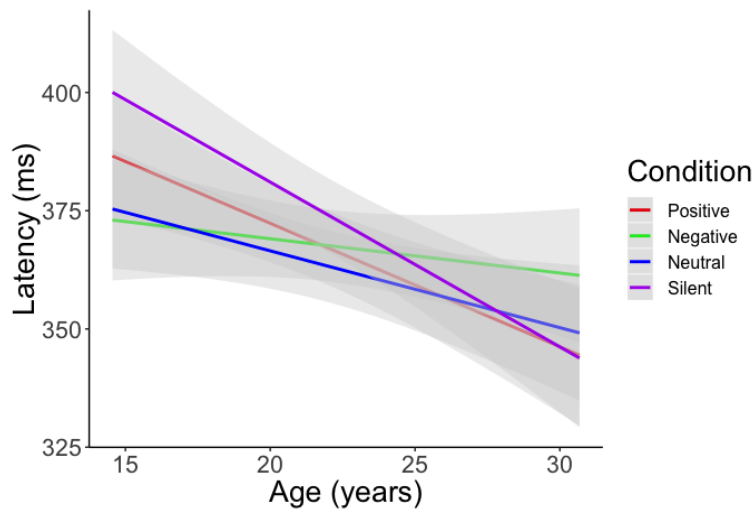
The positive condition represents sounds evoking high arousal and low valence, while the negative condition includes sounds with high arousal but low valence ratings. Neutral sounds were rated low on arousal, and somewhere in the middle on the valence scale.



**Figure 6: Line graph depicting the relationship between age and percentage of correct responses, separated by task condition and controlling for gender.**

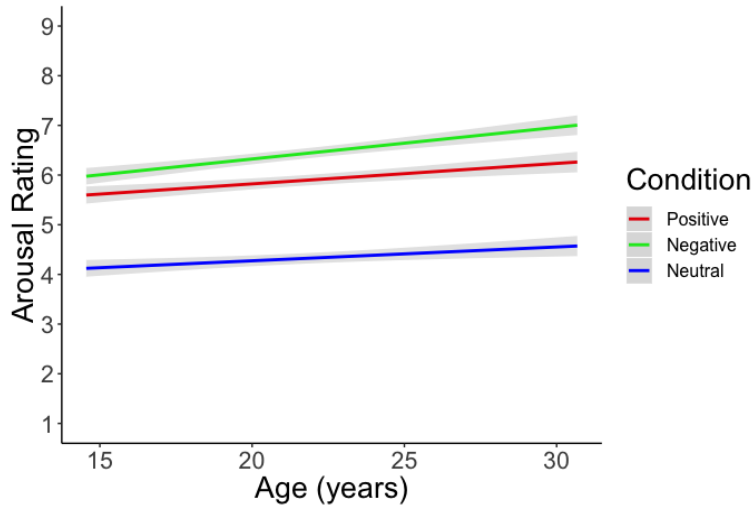
There was a significant effect of condition ( $\chi^2=9.2507$ ,  $p=0.02614$ ) and trending fixed effects of age ( $\chi^2=3.6321$ ,  $p=0.05668$ ) and gender ( $\chi^2=3.6080$ ,  $p=0.05750$ ). While no significant

age-by-condition interaction effect was found, the age effect was significant within the negative condition only ( $p=0.0270$ ).



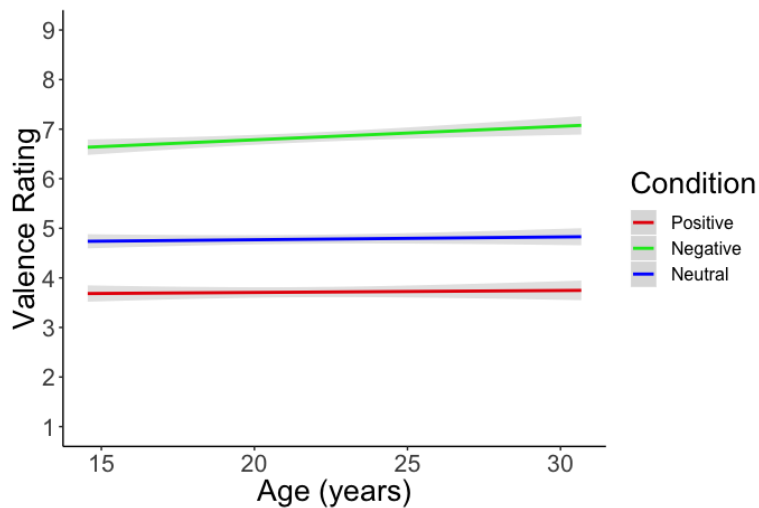
**Figure 7: Line graph illustrating the association between age and response latency for correct trials, separated by task condition and controlling for gender.**

The effects of age, condition, or sex were all nonsignificant, but a significant age-by-condition interaction occurred ( $\chi^2=11.6843$ ,  $p=0.008547$ ). This effect was driven by a significant age effect in the silent condition ( $p=0.0240$ ) and a trending age effect in the positive condition ( $p=0.0573$ ).

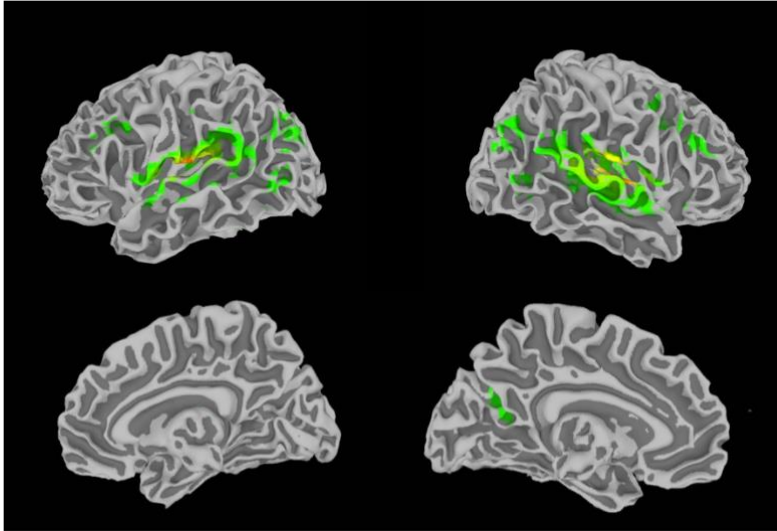


**Figure 8: Line graph representing the relationship between age and individual arousal ratings for sounds included in the task, separated by task condition and controlling for gender.**

This analysis yielded a significant effect of condition ( $\chi^2=1032.3165$ ,  $p<2 \times 10^{-16}$ ) and a trending effect of age ( $\chi^2=3.5116$ ,  $p=0.06094$ ), as well as a significant age-by-condition interaction ( $\chi^2=9.1437$ ,  $p=0.01034$ ). Within conditions, a significant age effect occurred in the negative condition only ( $p=0.0087$ ).



**Figure 9: Line graph showing the association between age and individual valence ratings for sounds included in this task, separated by task condition and controlling for gender.**



**Figure 10: A whole-brain voxelwise analysis examining the effects of condition, TR, age, and gender.**

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