

Neuroanatomical Correlates of Anxiety and Depression Tripartite Dimensions in Adolescents

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Abstract

This study aims to incorporate the Tripartite Model of Anxiety and Depression dimensions, proposed by Watson and Clark (1991) and administered with the Mood and Anxiety Symptom Questionnaire (MASQ), into continuous measures which can then be correlated with brain structure patterns in adolescents. During adolescence, the brain undergoes massive change, change which results in radical new ways of processing emotion and decision-making, and implicated in the onset of anxiety and depression. Through this methodology, we investigate the Dual Systems Model of adolescent development which suggests that two separate systems, the socioemotional system and the cognitive control system, develop either at different rates or at different times and that these differing rates are implicated in anxiety and depression development as well. Anatomical measures of mostly sensory processing regions correlated with anxious arousal and negative affect, supporting the overlap of those two dimensions and implicating sensory processing in anxiety. Anatomical measures of mostly cognitive processing regions in the prefrontal cortex (PFC) linked to learning, memory, and self-awareness correlated with positive affect. This finding supports the importance of PFC maturity in the modulation of and experience of emotional information. We speculate that positive affect is high during early adolescence, decreases in middle adolescence, then stabilizes or increases again as cognitive processing regions come online.

Introduction

Recent neuroscientific studies on anxiety and depression and neuroanatomy have focused primarily on clinical diagnoses (Schienle, et al., 2011; Strawn, et al., 2013; Arnone, et al., 2012). These categorical studies of anxiety and depression focus on the dichotomy between healthy and diagnosed individuals, ignoring continuous measures of symptomology. Binary diagnoses of anxiety and depression exclude conceptions of these disorders along a continuum. Researchers categorize participants into one or more groups based on the diagnostic requirements of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and often ignore subclinical symptoms altogether (American Psychiatric Association, 2013).

The experts in the fields of psychology and neuroscience have refined the DSM in its various forms over the last sixty years (APA, 2013). Despite its endurance and widespread use, the current DSM-5 lacks the power to accurately describe the complexities of anxiety and depression disorders. Designed primarily for clinicians to categorize individuals for treatment (APA, 2013), it is not a guide for understanding how neuroanatomy correlates with behavior. This is clear in the inclusion of comorbidity diagnoses in the DSM-5. Comorbidity occurs when a participant is diagnosed with two or more mental disorders. Up to 47 percent of adolescents diagnosed with depression are comorbidly diagnosed with an anxiety disorder (Essau, 2008) and comorbidity rates are almost twice as high amongst the general population (Angold, et al., 1999).

Three models exist to explain the overlap between depression and anxiety. The first model, the traditional model, dichotomizes anxiety and depression as two distinct and non-overlapping disorders (Gorman, 1996). The evidence of comorbidity seems to contradict the existence of this model in its current form. In apparent response to the traditional model, the

comorbid model suggests that anxiety and depression can co-occur at the same time (Gorman, 1996). The third model, the mixture model, advocates for the replacement of comorbid diagnoses with the diagnosis of a third disorder called the mixed condition of anxiety and depression (Gorman, 1996). Mixed anxiety and depressive disorder appeared in the DSM-IV as a combination of subthreshold anxiety and depression symptoms, but did not make the cut for the DSM-5. The DSM-5 accommodates the comorbid model and diagnoses individuals with either anxiety, depression, or both at the same time. However, the comorbid model most likely does not reflect the true nature of these disorders.

DSM-5 diagnoses do not preserve information about symptoms if these symptoms do not aggregate above defined thresholds. For example, individuals who worry excessively, but without three additional symptoms such as restlessness, fatigue, trouble concentrating, irritability, etc. do not qualify for a diagnosis of generalized anxiety disorder (GAD) (APA, 2013). These individuals, while subclinical, may suffer from impairment and have distinguishable neuroanatomical features from individuals with no excessive worry. Therefore, a more dimensional, rather than categorical, approach to anxiety and depression symptomology is required for identifying specific neurobiological underpinnings of these disorders.

The tripartite model of anxiety and depression aims to mitigate these problems through continuous measures designed to quantify and differentiate various dimensions of these disorders (Clark and Watson, 1991). According to the model, symptoms fall into one of three categories: negative affect shared by both disorders, positive affect of which low levels are linked to depression, and anxious arousal linked to anxiety. Negative affect (NA) “represents the extent to which a person is feeling upset or unpleasantly engaged rather than peaceful” (Clark and Watson, 1991). “Those high in NA will tend to report more negative affect across time [...] even

in the absence of any overt stress” (Watson and Clark, 1984). So, negative affect represents a pervasive disposition characterized by several emotions including, but not limited to nervousness, tension, worry, self-dissatisfaction, guilt, and anger (Watson and Clark, 1984).

Positive affect (PA) measures “pleasurable engagement with the environment” (Anderson and Hope, 2008). According to Clark and Watson, people express PA through high levels of energy, active engagement, delight, enthusiasm, interest, and pride (1991). Although positive and negative affect sound like opposites, the two measures do not necessarily inversely correlate. Low levels of NA do not translate automatically to high levels of PA and vice versa. For example, the absence of sadness (NA state) does not necessitate the experience of happiness (PA state). In fact, PA and NA associate with different health outcomes and social behaviors. Clark and Watson report that NA, health complaints, and perceived stress co-occur, while PA predicts extraversion and exercise (1991). Low levels of PA generally characterize depression and not anxiety, so anhedonia, a measure linked to low PA, discerns differences between anxiety and depression. However, we measure both PA and anhedonia in our study with subtly different questions. The PA questions relate to increased happiness, extraversion, and energy, while the anhedonia questions focus on low energy and interest combined with some NA. For example, one anhedonia question addresses thoughts of suicide which do not necessarily follow from only low levels of PA and could represent some combination of PA and NA.

The third category, anxious arousal (AA), or increased activity in the sympathetic nervous system, manifests in the body as rapid heartrate, dizziness, and shortness of breath (Anderson and Hope, 2008). AA symptoms more closely associate with anxiety disorders than depression. Like anhedonia and low positive affect, AA differentiates anxiety from depression.

Clark and Watson constructed these dimensions after extensive research as these dimensions they showed the highest levels of convergent and discriminative validity (1991). Convergent validity describes the extent to which two measures that should be related are in fact related. High convergent validity results when all measures of AA correlate with one another and with prevalence of anxiety disorders. Discriminative validity describes the extent to which two unrelated measures are in fact unrelated. The measures of PA and NA should not strongly correlate because these scales do not intend to measure the same dimensions of mental health. Low correlations of PA and NA indicate high discriminative validity of those measures and support the power of the branches of the tripartite model.

To parse out the three major dimensional categories defined by the Tripartite Model, Clark and Watson developed the Mood and Anxiety Symptom Questionnaire (MASQ) (1991). The questionnaire contains 90 items subcategorized into six subscales: general distress mixed (GDM), general distress anxiety (GDA), general distress depression (GDD), anxious arousal (AA), anhedonia (ANH), and positive affect (PA). The three general distress measures combine to construct the negative affect dimension (Clark and Watson, 1991).

Although researchers know little about how these dimensions specifically correlate with brain structure, they have conducted extensive research relating diagnoses of anxiety and depression, brain structure, and function. Anxiety is a relic of primal fear processing and response gone wrong (Canteras, et al., 2009). Healthy fearful responses include hyperarousal, hypervigilance, avoidance, somatic sensations such as stomachache, nausea, and headache, and even conscious experience of worry. Temporary occurrences of these responses help individuals avoid threats in the environment, such as when confronted by a grizzly bear in the woods.

However, long-lasting or inappropriate fear responses constitute many of the diagnostic criteria for anxiety disorders (APA, 2013).

Researchers posit that the same brain structures involved in fear processing and response are also implicated in anxiety (Canteras, et al., 2009; Etkin, 2009). In processing of fear, information relevant to negative stimuli travels through the thalamus, which relays sensory information to the amygdala (Etkin, 2009). For example, the amygdala receives emotionally relevant signals, such as loud sounds, growls, shouts, etc., directly from auditory systems via the thalamus (Lewis, et al., 2010). Upon receiving emotionally relevant information the amygdala evaluates its significance (Lewis, et al., 2010) and projects signals to other brain regions to initiate defensive action (Etkin, 2009). The insula, another subcortical region, also receives similar information and helps to regulate and monitor autonomic functions such as heart rate (Etkin, 2009). Both the amygdala and the insula show significantly more activation in individuals with anxiety disorders when shown pictures of fearful faces (Etkin, 2009), supporting theories which implicate fear processing in anxiety.

The frontal cortex, or the frontal part of the outer layer of the brain, also aids negative emotional processing. Etkin, et al. developed the emotional Stroop task to evaluate how the brain handles situations of emotional conflict (2006). In this task, researchers instruct participants to identify the affect associated with pictures of facial expressions (i.e. happy, fearful) while ignoring words associated with those facial expressions (i.e. happy, fear) displayed over the pictures (Etkin, et al., 2006). Trials in which the facial expression did not match the displayed descriptor (incongruent trials) correlated with higher levels of dorsomedial prefrontal cortex (dmPFC) activation (Etkin, et al., 2006). However, dmPFC activation decreased when

participants expected emotionally incongruent trials indicating that they recruited the dmPFC to resolve emotional conflict (Etkin, et al., 2006).

Anterior cingulate cortex (ACC) activation also correlated with emotional conflict regulation (Egner, et al., 2008; Mohanty, et al., 2007). Mohanty, et al. conducted further analysis to differentiate the function of the dorsal (upper) ACC (dACC) and the rostral (lower) ACC (rACC) (2007). Using the emotionally neutral color-word Stroop task, they showed that the dACC displayed more activation during incongruent trials and conversely that the rACC displayed more activation during negative emotion trials (Mohanty, 2007). These findings indicate that the dACC aids in more general cognitive regulation than the rACC, which specifically regulates emotion.

Evidence of connectivity between these regions and other known cognitive or affective regions also supports the cognitive/affective distinction between dorsal and rostral regions of the brain. Mohanty, et al. found that only activation of the dACC predicted activation in the dorsolateral PFC (dlPFC) (2007), an area involved in cognitive control and executive function (Snyder, 2013). Additionally, medial regions interconnect mostly with subcortical structures, such as the amygdala, which deal mainly with emotional or affective information (Koenigs and Grafman, 2009). More lateral regions of the frontal cortex interconnect with other lateral regions of the cortex associated with cognitive function (Koenigs and Grafman, 2009). Participants with depression show more activation in medial regions and less activation in lateral regions of the frontal cortex during rest than healthy individuals indicating that these regions differentially regulate depressive symptoms (Koenigs and Grafman, 2009).

The brain regions discussed so far construct a comprehensive view of anxiety and depression. Sensory systems (auditory, visual, etc.) send signals directly to the subcortical

regions of the brain. These regions include the amygdala and the ventral striatum which process negative stimuli and reward information, respectively. We consider these “affective” regions based on the information which they receive. Medial and rostral regions of the brain such as the rACC and the dmPFC in the frontal lobe interconnect with these subcortical regions and help regulate affective information. More lateral and dorsal regions of the frontal cortex process general cognitive information necessary for conscious experience and suppression of emotional information (Etkin, 2009).

Most of the aforementioned research focused on differences between adults diagnosed with anxiety and depression and healthy individuals. However, we know little about how young, developing, adolescent brains reflect the tripartite model. This study aims to incorporate the tripartite model dimensions from both depression and anxiety disorders into continuous measures which can then be correlated with brain structure patterns. Additionally, this study focuses on adolescence, a critical period where the brain undergoes massive change, change which results in radical new ways of processing emotion and decision-making, and implicated in the onset of anxiety and depression.

We might reason that anxiety and depression manifest differently in adolescents compared to adults because the regions implicated in anxiety and depression undergo important developmental changes during adolescence. The dual systems model describes a potential theory for the development of the brain during adolescence (Steinberg, 2010). The theory posits that two separate systems in the brain, the socioemotional system and the cognitive control system, develop in parallel during this time, but that their different rates of development may explain many different behaviors, cognitive phenomena, and affective processes.

The first system, the socioemotional system, includes limbic and paralimbic regions of the brain such as the amygdala and ventral striatum (Steinberg, 2010). Fearful-avoidance and reward-seeking behaviors involve this system. The socioemotional system begins growth and development in early adolescence. The second system, the cognitive control system, involves primarily the lateral prefrontal and parietal cortices (Steinberg, 2010). This system performs executive functions which regulate other systems throughout the brain. The broad concept of executive function includes tasks such as planning, goal setting, task switching, inhibition of distracting information, and decision-making (Snyder, 2013). As the cognitive control system develops it modulates the reward-seeking and fear-avoidance behaviors of the socioemotional system (Steinberg, 2010). Thus, behavior shifts focus from more affective goals to long-term goals and planning as the brain matures (Steinberg, 2010).

Development manifests differently in different brain regions in relation to the three anatomical measures of cortical morphometry: surface area, volume, and thickness. To understand what each anatomical measure represents in biological terms, we must explore the cellular organization of the cortex. Many neurons in the cortex align vertically, perpendicular to the pial surface, or the boundary between gray matter and cerebrospinal fluid which surrounds the brain (Rakic, 1988). In humans, the outer gray matter surface of the cortex folds into deep wrinkles, so neurons descend in columns perpendicular to the folded surface. Surface area is measured by inflating the heavily wrinkled surface into two dimensions where all sulci and gyri flatten to one uniform plane. Surface area informs researchers of roughly the number of neuron columns in perpendicular orientation packed into that two-dimensional space. Thickness measures the depth of the gray matter surface and relates to the average number of neuron cells

in each neuron column (Vijayakumar, et al., 2016). The product of surface area and thickness equals the third measure, volume, which relates to the total number of neuron cells in a region.

Throughout adolescent development the cortex undergoes a variety of distinct developmental processes by region related to thickness, surface area, and volume. The frontal and parietal regions of the cortex experience widespread reductions in thickness during adolescence (Vijayakumar, et al., 2016). Reductions in grey matter thickness during this time correlate with increases in white matter volume. White matter exists beneath gray matter and contains mostly axons which connect distributed regions of gray matter. White matter increases in volume with the myelination of axons, or the coating of axons with fatty tissue necessary for increased electrical impulse speed between distributed cortical regions. Surface area increases in these same regions, potentially the result of gyrification, or folding, of the gray matter surface (Vijayakumar, et al., 2016). Volume changes more variably with both increases and decreases in frontal and parietal regions occurring during adolescence (Vijayakumar, et al., 2016). The divergent growth rates of these two systems might lead to the development of anxiety and depression disorders.

This study, unlike many other studies of anxiety and depression focuses on relationships between the tripartite dimensions and structural neuroanatomy, rather than electrical activation or blood flow. Focusing on structure has its advantages. For example, structural measurements tend to be generally stable across time, less affected than functional activation by daily fluctuations in sleep, diet, mood, etc. Stability is important because this study focuses on stable and long-lasting anxiety and depression dimensions. Dimensions of anxiety and depression measure traits, consistent and stable characteristics, rather than states, temporary behaviors or feelings, so

structural measurements are more likely to correlate with these state-like dimensions than functional measurements.

Despite the advantage of structural measurements, most of our knowledge about how different regions of the brain perform cognitive and affective processes in anxiety and depression comes from functional studies. So, does knowledge gained from functional research apply to the current study which focuses only on structural information? Certainly, but the relationship between structure and function must be considered. In a recent review, Honey, et al. linked structure to function at cellular and network levels and reported that structural connectivity can predict functional connectivity between regions (2010). They also reported that “disturbances in [structural connectivity] ... become functionally expressed in disturbances of brain dynamics” in neuropsychiatric disorders (Honey, et al., 2010). This study indicates that structure and function are related, but how exactly structure and function interact in the human brain is not yet fully understood.

Considering the previous research, we hypothesize that anxious arousal, anhedonia, and negative affect will correlate with increased amygdala and ventral striatum volumes, decreased thickness of ventral and medial regions of the PFC, and surface area increases of the ventral and medial PFC.

Methods

Participants

A total of 51 adolescent participants (23 male, 28 female) were recruited from the Denver Metro area for this study. Participants were recruited from a list of willing participants taking part in ongoing studies conducted by Dr. Hankin at Denver University. Ages of participants

ranged from 14 to 22 and the mean age was 16.568 years old (SD = 1.590). These participants represented those who had completed two parts, an online survey questionnaire, from which we gathered estimates of our behavioral constructs of interest, and an MRI scanning visit, part of a larger continuing study conducted by Dr. Banich at the University of Colorado Boulder.

Exclusion criteria included MRI safety concerns such as metal in the body, pregnancy, or claustrophobia. Additionally, individuals who were non-English speaking, or who had a history of brain injuries or neurological disease or disability were excluded.

Upon recruitment, participants gave consent over the phone to fill out online questionnaires pertaining to mental health and demographic information, and agreed to come to the Center for Innovation and Creativity in Boulder for two visits. During the first visit, participants completed a battery of executive function tasks and diagnostic interviews. The second visit involved two MRI scanning sessions: one functional and anatomical scanning session and one spectroscopy scanning session; but this study will focus only on the anatomical scan data. Written informed consent was obtained before each experimental session and all experimental protocols were approved by CU Boulder's Institutional Review Board prior to the study.

Mood and Anxiety Symptom Questionnaire

Online questionnaires were distributed using the Qualtrics Insight Platform, which is an online data collection software, one week prior to their first experimental lab visit. One questionnaire was sent to each participating adolescent and all names were replaced with a unique identification number for that participant for the duration of the study. The questionnaire included the over 20 different surveys aimed at collecting information pertaining to mental

health, trauma, cognition, and personality; however, this study will focus on only one: The Mood and Anxiety Symptom Questionnaire (MASQ).

The MASQ contains 90 items related to mood and anxiety symptoms as defined by the DSM-V. Participants indicate the level to which they have experienced each particular item during the past week (1 = not at all, 5 = extremely). The ninety items divide into six different subscales (general distress: mixed, general distress: depressive symptoms, general distress: anxious symptoms, anhedonia, anxious arousal, and positive affect) relevant to the three branches of the tripartite model proposed by Clark and Watson (1991). The three general distress subscales combine to represent the negative affect branch of the tripartite model, while anhedonia/low positive affect and anxious arousal represent the other two branches of the model.

Imaging Data Acquisition

A Siemens Prisma 3 Tesla magnetic resonance imaging (MRI) system located at the Center for Innovation and Creativity at the University of Colorado Boulder was used to gather all structural data. A 32-channel headcoil was radiofrequency and transmission. Structural images were obtained via a T1-weighted Magnetization Prepared Rapid Gradient Echo sequence (MPRAGE) in 224 sagittal slices. Sequence parameters were as follows: 2.07ms echo time, 2400ms repetition time, 8-degree flip angle, 256mm field of view, and .8 mm³ voxel size.

Surface Based Morphometry

The brain is composed of three basic substances: white matter, grey matter, and cerebrospinal fluid/ dura mater. In the cortex, the outer layer of the brain, these three substances

form a gradient with the inner areas composed mostly of white matter, followed by a layer of mostly grey matter, then just beneath the skull a layer of cerebrospinal fluid and dura mater.

Surface based morphometry (SBM) is a process by which the layer of grey matter, which is composed mostly of neuron and glial cell bodies, is extracted and reconstructed. Cortical extraction and reconstruction were performed using FreeSurfer image analysis suite (freesurfer-Linux-centos4_x86_64-stable-pub-v5.0.0). In summary, FreeSurfer performs surface-based morphometry by fitting the brain volume to an average brain template, calculating and plotting points on the white matter surface, separating hemispheres, removing the corpus callosum and brain stem, and calculating and plotting the points on the grey matter surface between grey matter and CSF. Documentation and downloads of the FreeSurfer application can be found on the FreeSurfer website (<http://surfer.nmr.mgh.harvard.edu/>) and the surface-based morphometry pipeline is documented in detail by Dale, et al. (1998). Additionally, the extracted cortical surface was inflated to remove folding before analysis

Regression and Analysis

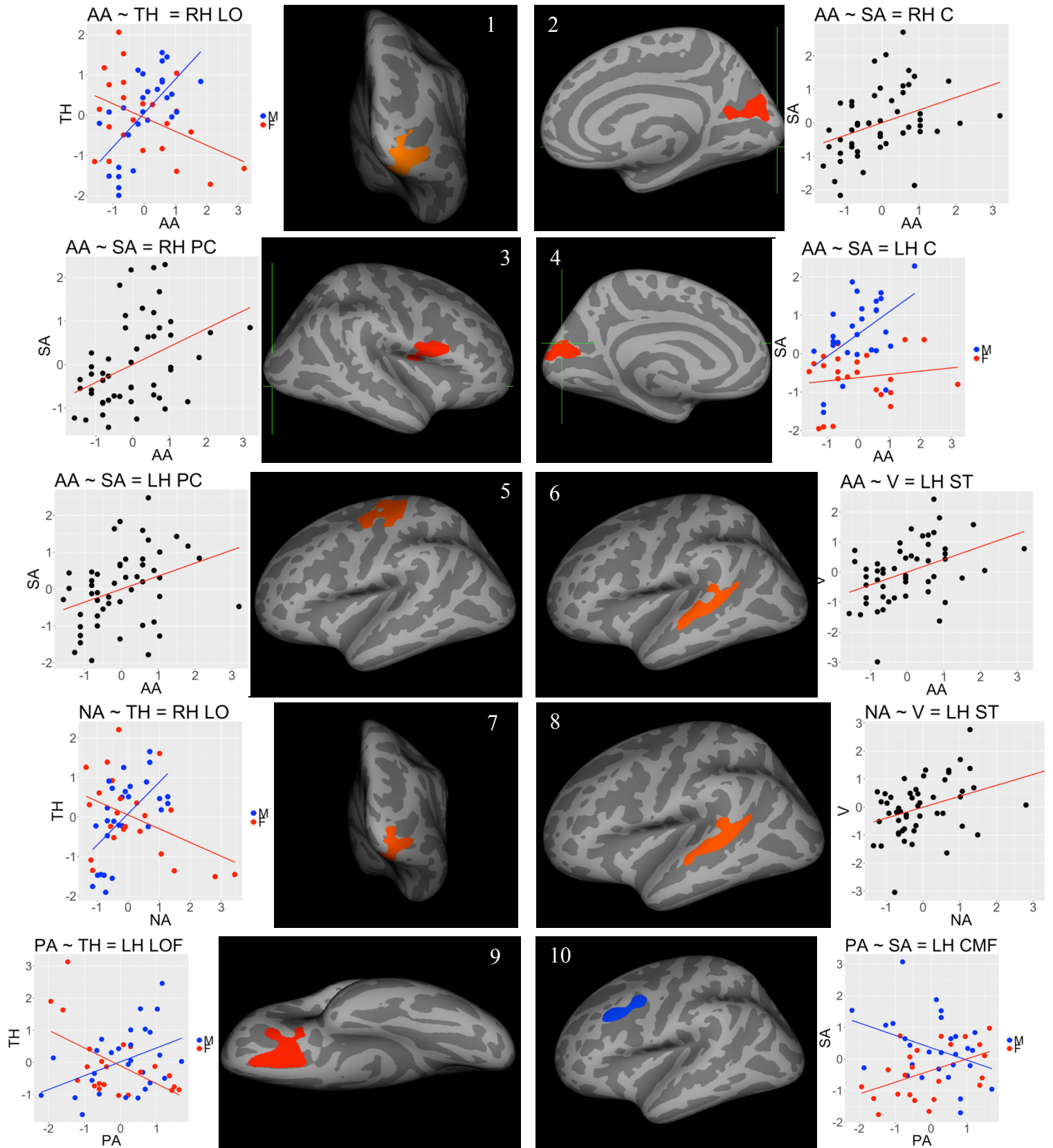
Regional SBM estimates, MASQ subscale z scores, total intracranial volume (ICV), IQ, and gender binaries were included in regression analysis. Initially significant areas were tested for multiple comparisons. IQ, ICV, and gender were controlled for during analyses.

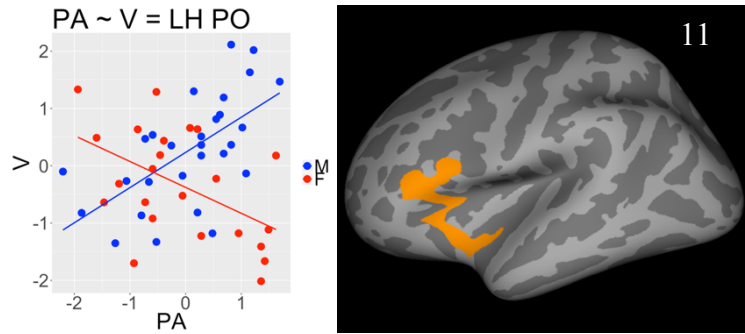
Results

Cortical Regions

Tripartite Dimension	Anatomical Measure	Region	Main Effect or Gender	Log(p)	Size (mm ²)	Plot
<i>Anxious Arousal</i>						
	Thickness	RH Lateral Occipital	Gender (males)	2.8539	1341.44	1
	Area	RH Cuneus	Main effect (positive)	1.5200	919.47	2
	Area	RH Precentral Gyrus	Main effect (positive)	1.3251	848.31	3
	Area	LH Cuneus	Gender (males)	1.5901	895.75	4
	Area	LH Precentral Gyrus	Main effect (positive)	2.2007	1576.34	5
	Volume	LH Superior Temporal Gyrus	Main effect (positive)	1.7305	449.89	6
<i>Negative Affect</i>						
	Thickness	RH Lateral Occipital	Gender (males)	2.1739	1134.06	7
	Volume	LH Superior Temporal Gyrus	Main effect (positive)	2.2291	1111.46	8
<i>Positive Affect</i>						
	Thickness	LH Lateral Orbitofrontal	Gender (males)	1.3242	816.90	9
	Area	LH Caudal Middle Frontal	Gender (females)	-1.8041	636.00	10
	Volume	LH Pars Opercularis	Gender (males)	1.3556	1148.43	11

Table 1: Significant correlations between tripartite dimensions and cortical region thickness, area, and volume.

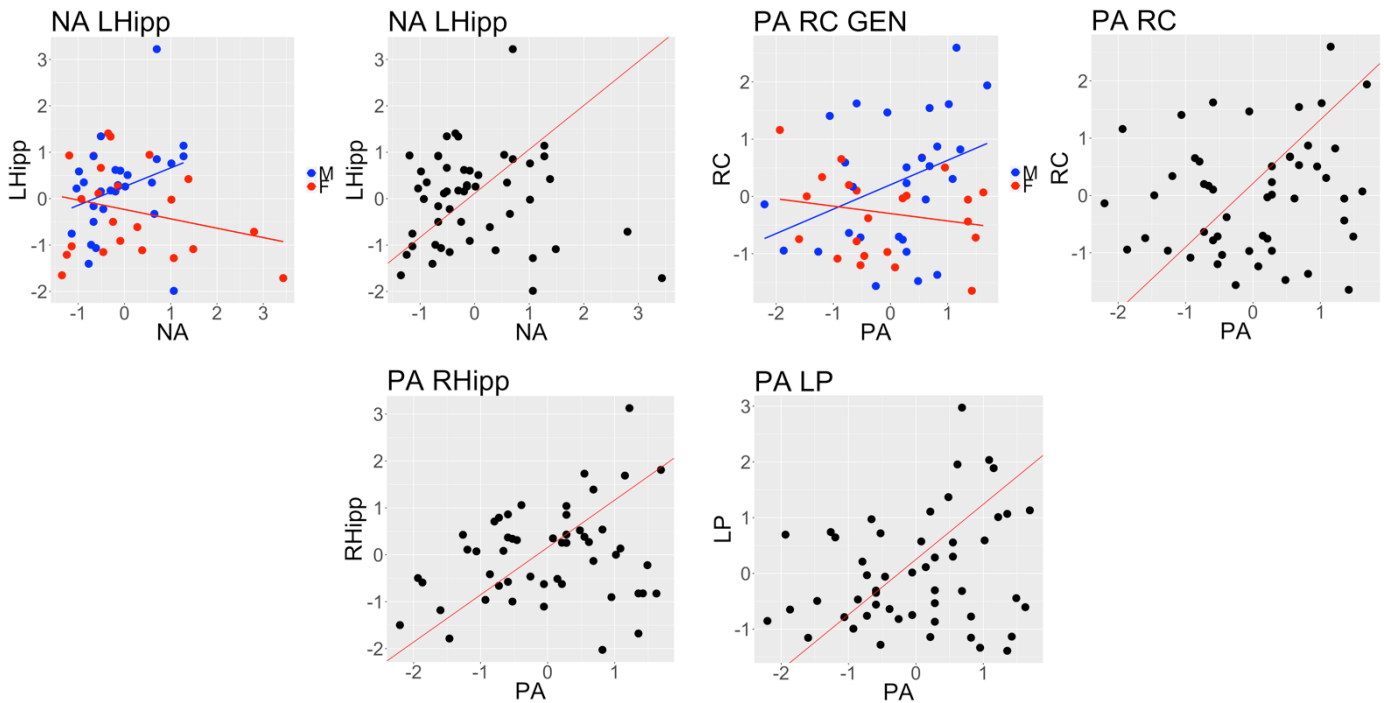




Figures 1-11: These scatterplots show the various significant correlations listed in Table 1. The tripartite dimensional subscale scores (AA=anxious arousal, PA=positive affect, NA=negative affect) are listed on the x-axis and the anatomical measures (TH=thickness, SA=surface area, V=volume) are listed on the y-axis of each individual graph. Where a gender effect is depicted blue=male, red=female. The titles include the hemispheres (right=RH, left=LH) and regions of interest (lateral occipital=LO, cuneus=C, precentral=PC, superior temporal=ST, lateral orbitofrontal=LOF, caudal middle frontal=CMF, pars opercularis=PO).

<u>Subcortical Regions</u>				
Tripartite Dimension	Region	Main Effect or Gender	p value	Plot
<i>Anxious Arousal</i>				
	Right Pallidum	Main effect (males)	2.8539	1
<i>Negative Affect</i>				
	Left Hippocampus	Gender (males)	0.0415	7
	Left Hippocampus	Main effect (positive)	0.052	8
<i>Positive Affect</i>				
	Right Caudate	Gender (males)	0.0407	9
	Right Caudate	Main effect (positive)	0.0234	10
	Right Hippocampus	Main effect (positive)	0.042	11

Table 2: Significant correlations between subcortical region volumes and tripartite dimensions.



Figures 12-17: Significant correlations between tripartite dimensions (AA=anxious arousal, NA=negative affect, PA=positive affect) and subcortical structures (RC=right caudate, RHipp=right hippocampus, LHipp=left hippocampus, LP=left putamen). On figures 13 and 15-17 red lines represent correlations controlling for IQ, age, and total intracranial volume and therefore do not align with displayed data points, which only relate volume to tripartite dimension.

Anxious Arousal

Anxious arousal subscale scores on the MASQ showed a gender effect for cortical thickness of the lateral occipital region in the right hemisphere ($\log(p) = 2.8539$; Figure 1) and for cortical area of the cuneus in the left hemisphere ($\log(p) = 1.5901$; Figure 4). Additionally, anxious arousal scores showed a positive association with area of the cuneus in the right hemisphere ($\log(p) = 1.5200$; Figure 2), precentral gyrus area in the left and right hemispheres ($\log(p) = 1.3251$ and Figure 5 and 2.2007 and Figure 3 respectively), and superior temporal gyrus volume in the left hemisphere ($\log(p) = 1.7305$; Figure 6).

Negative Affect

Negative affect subscale scores on the MASQ showed a gender effect for cortical thickness in the lateral occipital lobe of the right hemisphere ($\log(p) = 2.1739$; Figure 7) and volume of the left hippocampus ($p = 0.0415$; Figure 12) and negative affect showed a positive association with volume of the superior temporal gyrus in the left hemisphere ($\log(p) = 2.2291$; Figure 8) and with volume of the left hippocampus ($p = 0.052$; Figure 13).

Positive Affect

Positive affect subscale scores showed a gender effect with area of the caudal middle frontal region in the left hemisphere ($\log(p) = -1.8041$; Figure 10), volume of the pars opercularis region in the left hemisphere ($\log(p) = 1.3556$; Figure 11), and volume of the right caudate ($p = 0.0407$; Figure 14). Additionally, positive affect showed a gender effect for cortical thickness in the lateral orbitofrontal region in the left hemisphere ($\log(p) = 1.3242$; Figure 9) and volumes of the right caudate ($p = 0.0234$; Figure 15), left putamen ($p = 0.0342$; Figure 17), and the right hippocampus ($p = 0.042$; Figure 16).

Anhedonia

No significant relationships were found for anhedonia subscale scores.

Discussion

In painting the big picture, let's start at the bottom with the most affective regions of the cortex. Thickness of the right hemisphere lateral occipital lobe (RHLO) showed a gender effect with both AA and NA scores such that boys showed a positive relationship and girls showed a negative relationship. Cortex development in females occurs one to two years before males (Lenroot, et al., 2007) and thickness in the RHLO increases on a negative quadratic curve (inverted U-shaped) during adolescence (Vijayakumar, et al., 2016). For girls, who lie further along the curve (on the downward slope), the thinner the RHLO the more mature. Conversely, boys lie on the increasing slope of the curve where a thicker RHLO marks more maturity. Functionally, the RHLO specifically processes visual information. The symptoms measured by AA and NA questions on the MASQ, such as sensations of fear, nervousness, and anticipation of negative outcomes, recruit visual processing to identify and mitigate threats in the environment. Additionally, association of the cuneus, another region important for visual processing, with AA supports these assumptions.

The superior temporal gyrus (STG) supports another modality, hearing. The auditory cortex, part of the STG in the left hemisphere, receives sound information relevant to communication (Purves, et al., 2012). Both NA and AA scores positively associated with STG volume (Figures 6 and 8) and people high in those dimensions may additionally require speech and general sound processing to process threats in the environment.

The superior temporal gyrus also plays an important role in the perception of emotional faces (Hoffman and Haxby, 2000) and dynamic movements of faces (Bernstein and Yovel, 2015). Navigating a highly social world requires the ability to identify emotions in others, through faces and voices. For those suffering from anxiety, the need is potentially twofold. In

disorders like social anxiety disorder, individuals agonize over how others perceive them and reading facial cues in others is one way to measure social scrutiny. Superior temporal gyri mature relatively late (Gogtay, et al., 2004) with inverted U-shape increases in volume throughout adolescence (Vijayakumar, et al., 2016). The positive associations we found (Figures 6 and 8) suggest that our participants were still maturing along the increasing side of the development curve and those high in AA and NA recruited the superior temporal gyri to process additional affective information.

The only two regions associated with NA are also associated with AA. This is not surprising since general distress: anxiety (GDA) is one of the three component scales that make up NA. The GDA subscale contains questions similar to AA questions, thus the NA composite score and the AA subscale are highly correlated. For example, one GDA question asks whether participants “felt keyed up.” A related AA question asks whether their “muscles twitched or trembled,” which is one possible physical manifestation of “feeling keyed up.”

Many of the AA questions ask about physical bodily manifestations of anxiety, thus the precentral gyrus (PC), which directs motor action, shows a correlation with AA. Surface area of the PC in both hemispheres correlates with AA scores (Figures 3 and 5). The right hemisphere PC region of interest (ROI) overlaps with brain areas responsible for initiating facial movements (Purves, et al., 2012). In the left hemisphere, this ROI directs muscle movement in the trunk, arm, and hand (Purves, et al., 2012). These ROIs explain reports of fidgeting, trembling, and shakiness associated with AA. The periphery of this ROI overlaps with the somatosensory cortex, which receives feedback from the body about temperature, texture, pain, and touch (Purves, et al., 2012). The precentral gyri mature very early in adolescence (Gogtay, et al., 2004)

with linear increases in surface area (Vijayakumar, et al., 2016), indicating that those high in AA require more mature precentral gyri.

So far, the ROIs have revealed one important revelation: those high in AA and NA require mature systems to process sound, vision, and touch. Considering the AA and NA subscales, this revelation makes sense. The AA questions and the related NA questions describe fear processing gone wrong. Social anxiety, specific phobias, separation anxiety, all these disorders require attention paid to the outside world to gather information about the emotions of others and threats in the environment. For those battling anxiety, life becomes an endless struggle to identify and mitigate threats, threats in the form of social scrutiny, physical harm, and the commitments of day-to-day life.

Conversely, the ROIs associated with PA process cognitive information that regulates emotion. Volume of the pars opercularis (PO), showed a significant gender effect with PA (Figure 11). Parts of the PO are specifically activated when people view and imitate emotional facial expressions (Hennenlotter, et al., 2005). Researchers suggest that learning occurs in the PO via mirror neurons, which fire not only when performing motor action, but also when observing that same motor action performed by someone else (Hennenlotter, et al., 2005; Purves, et al., 2012). Thus, mirror neurons in the PO help us consciously perceive and experience positive affective facial expressions. Other studies have shown that even unconscious exposure to emotional facial expressions can trigger motor responses (Dimberg, et al., 2000) and that smiling, even when forced, can increase positive affective responses (Strack, et al., 1988). The ROI centered around the PO also overlaps with the insula, a region hidden in the fold between the frontal and temporal lobes and associated with body awareness (Critchely, et al., 2004).

Girls show decreased PO volumes associated with higher PA scores, whereas boys show the opposite effect. Initially, we might conclude that this area is more important for the manifestation of PA in male cognition than females. However, because the volume of this region decreases during adolescence (Vijayakumar, et al., 2016), potentially a dynamic function exists between volume of the PO and PA during adolescence. Boys early in the course of development presumably have the largest PO volumes and also have high PA scores. Generally, PO volume decreases throughout development and boys score lower on the PA subscale, overlapping with girls (one to two years ahead developmentally) who also have low PA scores. After this decline in PA, scores increase again for girls as PO volume continues to decline. Therefore, we consider the possibility that PA scores change based on a U-shaped curve during adolescent development with higher scores present in early and late adolescence (See Illustration 1).

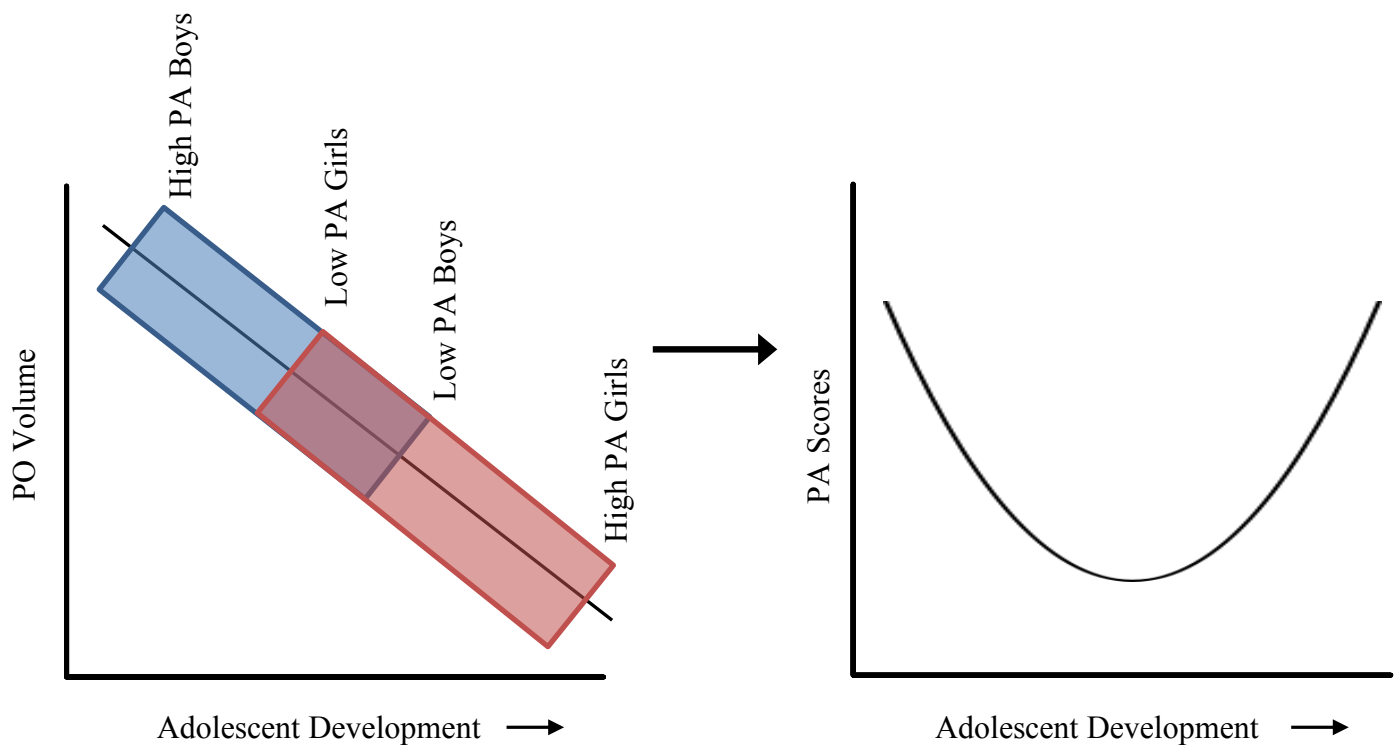


Illustration 1: Potential relationship between PA and adolescent development extracted from PO volume gender differences. PO volume decreases linearly during adolescence, high PA boys have largest volumes

Does PA really change that much or at all during adolescence? The answer is probably yes. Larson, et al. found that, generally, reports of PA decrease and reports of NA increase during early adolescence (2002). Additionally, PA and NA reports stop changing and bottom out at around the 10th grade (Larson, et al., 2002). Other research has found that the correlation between self-awareness (linked to the OP region) and depressed mood is highest during middle adolescence (Chen, et al., 1998). Neither of these studies necessarily support the claims made above. In fact, if self-awareness, linked to the OP, correlates with depressed mood, then PA scores should continue to decrease throughout adolescence as the OP region matures. However, as Larson, et al. points out they do not continue this downward trend, stabilizing in late adolescence (2002). Other frontal regions correlated with PA will help to construct a bigger picture.

We found an opposite gender effect for PA in the caudal middle frontal gyrus region (CMF), involved in high level cognitive function such as memory and executive function (Diamond, 2013). The PA questions on the MASQ focus on self-confidence, pride, perceived social competence, and happiness. Thus, girls, rather than boys, may internalize thoughts using the CMF to build their self-image. Conversely, those girls low in PA might underutilize the CMF. The CMF is part of a larger region called the dorsolateral prefrontal cortex (dlPFC). Increased activation in the dlPFC during rest supports high level cognitive functioning and predicts lower levels of clinical depression (Koenigs and Graham, 2009). Therefore, when this system comes online at some point during adolescent development it likely contributes to the higher PA scores related to lower levels of clinical depression.

The third region associated with PA scores was the orbitofrontal region (OF). As previously mentioned, cortical thickness generally decreases during adolescence and the orbitofrontal (OF) region is no exception (Figure 9). The OF receives projections directly from the amygdala which conveys information about the emotional significance of events (Barbas, 2007). The OF then communicates with other lateral prefrontal regions and projects signals back down to the amygdala to initiate actions to handle emotional events (Barbas, 2007). Thus, the gender effect, which reveals thicker lateral OF regions in males than females, supports the same PA-developmental curve mentioned earlier (Illustration 1). Boys with the thickest OF regions and girls with the thinnest OF regions (the poles of the developmental timeline) show the highest levels of PA, while those in the middle show decreased levels of PA.

Intimately interconnected with the OF is the caudate, part of the subcortical structure known as the basal ganglia. Emotional information flows into the basal ganglia and only the strongest inputs effect actions like working memory updating and moving muscles (O'Reilly, 2012). In the OF, the basal ganglia update information about the emotional significance of events, and in the CMF (caudal middle frontal gyrus mentioned earlier), the basal ganglia update working memory items. No matter the function, the basal ganglia play a significant role in learning and effecting action linked to positive outcomes. Significant associations between caudate volume and PA scores could indicate several possibilities. One possible interpretation says that effective learning is crucial for getting what you want in life, especially in adolescence, and getting what you want is linked to PA. In fact, many of the PA subscale questions focus on personal measures of success, success dependent on effective learning. Another explanation suggests that only with context dependent information from the basal ganglia can the dlPFC effectively downregulate negative affective information and upregulate PA information.

For NA, volume of the left hippocampus correlates with increased subscale scores primarily for males. Surprisingly, this finding seems to contradict previous research which found reduced hippocampus volume associated with subclinical depression scores for males (Spalletta, et al., 2014). Conversely, PA scores were associated with increased right hippocampus volume. The left and right hippocampi serve as the primary memory stores for the brain (O'Reilly, 2012). and are not completely functionally homologous. The right hippocampus is associated with spatial memory or memory of locations, whereas the left is associated with episodic memory (Burgess, et al., 2002). It's hard to draw conclusions from this finding especially since it appears to contradict previous research, but we might conclude that those high in NA recruit the left hemisphere to ruminate on old memories. Rumination is a cognitive process closely linked to anxiety, yet the details are beyond the scope of this current investigation.

In conclusion, the results reveal several important points about adolescence, neuroanatomy, and anxiety and depression dimensions of the tripartite model. First, AA and NA overlap in their neuroanatomical correlates. This makes sense since one third of NA comes from anxiety specific symptoms related to AA. Both dimensions include fear and body sensation related questions accounted for by significant correlations with sensory processing regions. Further investigation is needed to determine, on the depression side of the spectrum, how the neuroanatomical correlates of anhedonia overlap with NA. Second, PA scores correlate with regions implicated in cognitive processing. As adolescents develop, frontal cortex regions come online. These regions are potentially important for downregulating negative emotion, body awareness, learning, and cognitively constructing positive self-images. Subcortically, the right caudate helps update emotional significance information and working memory information necessary for learning. Effective learning likely leads to self-actualization, success, and down

regulation of irrelevant negative stimuli. This study also stimulates speculation about how PA changes during adolescence and how these changes are linked to frontal lobe development. Drawing conclusions about the course of brain development can be dangerous without the aid of a longitudinal study design. The current study speculates on adolescent development by using knowledge gained from previous research. However, this is no substitute for longitudinal data gathered from a single sample of adolescents. Further longitudinal research of similar design will help to better understand the exact changes that occur in PA, NA, anhedonia, and AA and how they relate to development of the adolescent brain over time.

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