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RISK PROFILES FOR ADOLESCENT INTERNALIZING PROBLEMS

A Dissertation Presented

by

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of

The University of Vermont

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ABSTRACT

Objective: Internalizing problems are commonly diagnosed during adolescence, and are associated with distress, impairment, and negative mental health outcomes in adulthood. Thus, there is a critical need to characterize adolescents who are at the highest risk for escalating to clinical levels of internalizing problems while extending current literature and incorporating both biological and environmental predictors. This study aimed to characterize risk profiles for fourteen-year-old adolescents who developed clinical levels of internalizing (High Internalizing [HI]) problems by age nineteen, using brain, genetic, personality, cognitive, life history, psychopathology, and demographic measures. The study also examined whether there were functional and structural brain differences in three groups of adolescents on select regions of interest (ROIs) on the Faces Task, Stop Signal Task, and Modified Incentive Delay Task.

Method: Participants were 91 adolescents who met clinical criteria for at least one Anxiety and/or Depressive Disorder by age 19 and 1,244 controls who varied in symptom level but did not reach clinically-diagnostic criteria. Ten-fold cross-validated logistic regression using elastic net regularization was used to identify risk profiles associated with high levels of internalizing symptomatology. To examine group differences in regions of interest on three fMRI tasks and in gray matter volume, ANCOVAs were conducted. The three groups were: 1) adolescents who never met HI criteria (Controls), 2) those who met HI criteria in middle adolescence (Middle Onset), and 3) those who met HI criteria in late adolescence (Late Onset).

Results: Logistic regression identified 13 variables from personality, psychopathology, life events, and functional brain variables to predict High Internalizing symptoms (mean AUC 0.78, $p < .0001$). ANCOVAs showed there were several ROIs that demonstrated main effects of Time, and one main effect of Group during response inhibition in the left inferior frontal gyrus, triangular part (*pars triangularis*), with participants in the Middle Onset group showing increased activation levels compared with the Control group. There were no other significant main effects of Group or Time x Group interactions.

Conclusions: These findings give insight into personality, psychopathological, and brain-related factors that are associated with high levels of internalizing symptoms, highlighting the importance of including biological variables in conjunction with psychosocial variables when examining risk factors for internalizing problems. Results also suggest an association between activation in frontal cortex and parietal lobe regions during response inhibition and higher internalizing symptoms in late adolescence. Between-group activation and volumetric ROI comparisons generally yielded main effects of time, confirming prior evidence that activation levels and GMV continue to change over the course of adolescence.

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CHAPTER 1: INTRODUCTION

Rates of adolescent internalizing disorders (i.e., anxiety and depressive disorders) are concerning; according to twelve-month prevalence rates from the National Comorbidity Survey Replication Adolescent Supplement (NCS-A), 10% of adolescents ages 17-18 meet criteria for Major Depressive Disorder or Dysthymia, and 25% meet criteria for an anxiety disorder [1]. Internalizing disorders are commonly diagnosed during adolescence, with evidence suggesting that they persist into adulthood [2, 3]; in fact, there is significant evidence that youth internalizing problems are associated with negative mental health outcomes in adulthood [4, 5]. Although research examining anxiety and depression separately has yielded critical information regarding risk factors and outcomes for each disorder, support for general internalizing factors has also been voiced [6]. Moreover, anxiety and depression are commonly comorbid and have been shown to share several common risk factors [7, 8], and evidence suggests that youth with depression may exhibit elevated rates of anxiety disorders and *vice versa* [9]. As such, the current study is guided by an overarching internalizing disorders perspective that accounts for frequent comorbidity rates of anxiety and depression, rather than by unique and separate predictors of anxiety and depressive disorders. Given the prevalence and persistence of internalizing disorders in adolescence, there is a critical need to characterize adolescents who are at the highest risk for escalating to clinical levels of internalizing disorders, and more research is needed to identify both biological and environmental predictors associated with clinical levels of impairment in community samples of adolescents.

This study specifically addresses the need to examine both biological and environmental risk factors associated with clinical levels of impairment by drawing from a dataset that includes functional and structural neuroimaging data, behavioral, neuropsychological, and genetic data [10]. Importantly, this study addresses concerns regarding non-reproducible and overfit findings associated with analyzing large multivariate neurobiological datasets [11] by utilizing a cross-validation analytic approach. The goals of the study are to: 1) generate risk profiles that characterize adolescents at the highest risk of endorsing clinically significant internalizing symptomatology at age 18-19 using a multimodal approach, and 2) to examine brain differences in total grey matter volume and task activation in individuals who endorsed clinically-significant internalizing symptomatology at age 19 and those who did not.

1.1. Risk Factors: Anxiety Disorders

Numerous domains have consistently emerged in the literature as risk factors for anxiety. Females present with higher rates of anxiety than males in several youth samples using self-reported measures of anxiety [12-14], and sex by age interactions have been demonstrated in adolescent anxiety disorders, with older females reporting higher levels of anxiety [15]. Puberty status is also associated with increased risk, with studies showing that anxiety and internalizing symptoms are more common with earlier puberty in adolescent females [16, 17]. Temperament and personality traits have been implicated in anxiety, with Negative Affect, Behavioral Inhibition, and Neuroticism appearing consistently. Research on the tripartite model of emotion [18] has produced substantial evidence that Negative Affect is a risk factor for both anxiety and mood disorders [19-22]. Behavioral inhibition also has robust associations with anxiety in youth [23-25], and

Neuroticism has been shown to be a common factor in internalizing disorders as a whole [26, 27]. Attentional bias has also been evident in anxious youth, such that they may selectively attend to threatening information over nonthreatening information [28].

Research in the field of Affective Neuroscience has provided evidence for neural underpinnings of anxiety. Anxious youth exhibit greater right amygdala activation when viewing angry faces [29] and demonstrate increases in right amygdala responses while viewing fearful expressions and providing fear ratings [30]. Youth with social anxiety have demonstrated greater amygdala activation when viewing pictures of peers rated as less desirable, as illustrated in a study using a simulated web-based chat room [31]. Further, youth with anxiety disorders, compared with controls, have exhibited increased amygdala activation while viewing emotional faces [32] and have shown increased amygdala connectivity with prefrontal cortex regions when viewing angry faces [29, 31]. Further, adolescents with Generalized Anxiety Disorder, Social Anxiety Disorder, and Separation Anxiety Disorder, compared with healthy controls, exhibit increased activation in the left orbitofrontal cortex, which is implicated in guiding behavior and decision-making [33]. There is also evidence for volumetric amygdala differences in youth with anxiety, such that larger right and total amygdala volumes have been found in anxious youth as compared to controls [34]; however, there is also evidence to the contrary, with some studies showing reduced amygdala grey matter in youth with anxiety disorders as compared with controls [35], and some showing no association between the two [36]. Research on the function and structure of the hippocampus in anxious youth has also yielded inconsistent results. Trait anxiety in adolescent females has been shown to be negatively correlated with hippocampal activity during a negative emotion-processing

task [37]; however, it is notable that the hippocampus has also been implicated in populations characterized by internalizing disorders as a whole. For example, in an adolescent sample exhibiting both depression and anxiety, greater hippocampal activation while rating fear was found in those with anxiety and/or depression compared with controls [38]. Additionally, total internalizing problems (as measured by the Child Behavior Checklist) has been found to be inversely related to hippocampal volume in a sample of typically developing youth ages 8-17, regardless of gender, informant, or age [39]. The role of genetic influences contributing to anxiety has also become an increasingly important field of research. Genome-wide association studies and candidate gene approaches have identified several genes and polymorphisms that may be associated with anxiety [40-42].

In addition to neurobiological factors, the current study also explores environmental factors that may contribute to the development of internalizing disorders. With regard to demographic variables, research on racial, cultural, and ethnicity differences in anxiety has been inconsistent, with some studies showing differences in anxiety symptoms based on racial identity and some showing no differences [43]. Evidence regarding the relationship between socioeconomic status and anxiety symptoms in youth has generally shown an inverse relationship [44, 45]; however, some evidence exists for a positive association between high socioeconomic status and high anxiety [12].

Stressful life events are associated with increased anxiety sensitivity [46] and anxiety disorders [47]. Further, stressful life events may even play a role in the onset of anxiety disorders [48], and children with anxiety disorders may be more likely to experience early stressful life events [49].

Existing literature on the influence of parenting and family characteristics demonstrates consistent associations between parent and child anxiety, such that risk of a child anxiety disorder is more than three times greater when a parent has a lifetime history of anxiety, and more than four times greater when a parent currently has anxiety [50, 51]; however, careful review of studies involving family and parenting variables illustrates the challenge in synthesizing specific patterns due to variations in populations studied, measurement strategies, definitions of outcome measures, and genetic versus environmental influences [52]. That being said, strong evidence for the association between anxiety and parental overcontrol has been found [53, 54]. In fact, McLeod and colleagues' (2007) meta-analysis of parenting and youth anxiety found that parental control was more strongly associated with anxiety than parental rejection; however, it is notable that parenting accounted for only 4% of the variance in child anxiety.

1.2. Risk Factors: Depression

Individuals who develop depression in adolescence may be particularly at risk of impairment in the future, as early onset depression has been shown to be more severe than later onset depression, and is associated with increased frequency and duration of depressive episodes, as well as with increased suicidality [55]. Several biological characteristics have been shown to relate to the development of clinical depression. Sex has been implicated as an important risk factor, such that by early adolescence, rates of depressive disorders increase in females to roughly twice the rate as males [3]. The transition through puberty also highlights differences between adolescent females and males. Pubertal stage carries risks for both the onset and persistence of depressive symptoms in females [56]. Similarly to associations between puberty status and anxiety,

puberty status may fall into both biological and environmental domains, because females may also experience heightened environmental risk factors during puberty due to greater exposure to social challenges [57], and may cope differently with stressful life events [58].

There is evidence for an association between temperament and personality traits and depression in adolescents, with Negative Affect, Neuroticism, and Behavioral Inhibition having been consistently implicated in the literature [59, 60]. High Negative Affect has been shown to have a strong association with depressive symptoms in adolescence [60, 61] and may moderate the impact of environmental factors (e.g. peer victimization, negative parenting) on depression [62, 63]. Neuroticism has also been implicated in depression [22]. Aldinger and colleagues (2014), in a longitudinal study of adolescents in a community sample, showed that adolescents with higher Neuroticism had a 14-fold increased risk for depression and a 7-fold risk for anxiety disorders at the age of 25, implicating Neuroticism as an important risk factor for the development of internalizing problems [64]. Additionally, Behavioral Inhibition is a risk factor for depression [65, 66]. Emotion regulation may also be compromised in depressed youth [67] and has been shown to predict later depressive symptoms [68].

Emotion processing and attentional bias deficits in youth have been shown to be associated with depression. Youth with depression may perceive more anger and less joy in low intensity facial stimuli [69] and may inaccurately identify parents' emotions during parent-child interactions [70]. Further, evidence suggests that depressed youth may selectively attend to negative stimuli [71].

Research investigating neural underpinnings of depression has generally examined brain structures that are associated with the response to, and detection of, emotional information, with much of the research investigating the amygdala and hippocampus. The amygdala, a part of the limbic system that plays a role in fear, has been implicated in individuals with internalizing problems; however, there are mixed results with regard to patterns of amygdala function and structure in adolescents with such symptoms [72]. In depressed youth, some evidence exists for heightened amygdala activation during tasks with emotional stimuli [73], while some findings have shown reduced amygdala activation [32]. Volumetric studies also show mixed results, with some evidence for reduced amygdala volumes in depressed adolescents, compared with healthy controls [74] and other evidence for no group differences [75, 76]. The hippocampus, involved in emotional responding and the consolidation of information into long-term memory, is believed to be dysregulated in individuals with depression. Greater hippocampal activation during emotional tasks has been shown in adolescents with anxiety and/or depression, compared with healthy controls [38]. Studies involving adolescents with depressive symptoms [77], at risk for depression [78], and with a family history of depression [75] have found reduced hippocampal volumes compared with controls; however, it is possible that reductions in hippocampal volumes may be associated with the genetic and environmental effects that might precede depression [79]. Advances in genetic research have offered new evidence regarding potential genetic contributions to depression [80-82], although much of the literature is focused on adults. Studies regarding genetic factors and their impact psychopathology have increasingly focused on candidate genes and polymorphisms (e.g., 5-HTTLPR, BDNF), while other

studies have yielded evidence for gene-environment interactions, dysfunctional neural circuits underlying emotion processing, and biological stress responses (e.g., HPA axis functioning).

Environmental factors also have been shown to contribute to the development of depressive symptoms. Studies examining systematic differences in depression by race and ethnicity have shown mixed evidence, perhaps due to the difficulty in measuring whether such effects result from true biological differences. Some research indicates no differences in rates of depressive symptoms between racial categories [83] and some suggests that African-American, Hispanic/Latino/a, and Asian-American populations have higher rates of depressive symptoms compared with White Americans [84, 85].

Evidence for relationships between sociodemographic variables and depressive symptoms in adolescents has also been inconsistent. Twenge and Nolen-Hoeksema (2002), in a meta-analysis examining depressive symptoms in adolescent samples, found that there was no clear association, and the NCS-A study [84] also reported a lack of association between poverty and lifetime depressive disorders in youth.

Research has shown that stressful life events are robustly associated with depression [86, 87]. In fact, youth onset depression is strongly associated with childhood family adversity, parental neglect, and problematic peer relationships [88, 89]. Further, stress in a variety of contexts (e.g., family, school) may contribute to the maintenance of depression over time [90]. Additionally, interpersonally stressful events experienced by depressed youth are associated with impaired relationships with peers, which may then contribute to depressive symptoms [91, 92].

Parenting and family characteristics also contribute to vulnerability for depression. Across development, a family history of depression is one of the most robust risk factors for youth depression [87], a finding that is also supported by heritability estimates. Select parenting behaviors are associated with later depression in youth; for example, parental psychological control is associated with later depression in youth [93], and critical parenting styles may predict the onset and maintenance of depression [94, 95]. McLeod and colleagues' (2007) meta-analysis of parenting and youth depression found that parental rejection was more strongly associated with depression than parental control, but that parenting accounted for only 8% of the variance in depression [54]. Notably, evidence exists for a positive association between parental rejection and control and both anxiety and depression [96].

1.3. Study Objectives and Hypotheses

As reviewed, there is a plethora of identified risk factors from a variety of separate domains for the development of internalizing disorders. The current study is novel in that it not only utilized a multimodal approach to examine risk factors that characterized symptom level within a longitudinal design using data at age 14 (Baseline), age 16 (Follow-Up 1, hereafter FU1), and age 18-19 (Follow-Up 2, hereafter FU2), but also examined between-group comparisons of individuals who meet clinical cutoff criteria for internalizing problems by FU2; thus, this study draws from and expands upon previous work by allowing an opportunity to identify pathways that lend insight regarding possible etiological mechanisms over three time points. Further, the current study addresses these questions within an important developmental span of ages 14-19, and addresses many methodological concerns associated with the inclusion of biological

data in analysis. Results will be valuable for increasing the current understanding of biological (e.g., neural and genetic) influences on internalizing disorders, as the study utilizes a large sample size, a prospective design, and an analytic method that assesses the replicability of results.

The first objective of this study is to generate risk profiles that characterize adolescents at the highest risk of endorsing clinically-significant internalizing symptomatology at FU2, using a multimodal approach. As reviewed, there are several identified risk factors from a variety of separate domains for the development of internalizing disorders. Notably, a previous analysis predicting clinical levels of internalizing problems at FU1 in 93 adolescents from the IMAGEN sample found previous anxiety levels (increased Separation and Generalized Anxiety), demographic variables (being female, more advanced puberty status), personality traits (higher Neuroticism), and structural and functional brain differences (increased grey matter volume (GMV) in the right putamen, increased activation in the right medial temporal pole while viewing angry faces, and reduced response in right precuneus during reward anticipation) to be associated with clinically-significant internalizing problems two years later [97]. Thus, given that this analysis will draw from the same domains, the following domains and variables are hypothesized to predict internalizing symptoms at FU2: personality traits (e.g. adolescent Neuroticism), biological variables (e.g. sex, pubertal status), environmental influences (e.g. stressful life events), and activation differences (e.g., response to faces showing anger during the Faces Task).

The second objective of the study is to examine potential brain differences at Baseline and FU2 in task activation and gray matter volume (GMV) in individuals who

endorse clinically-significant internalizing symptomatology at FU2, based on the time period in adolescence when they met clinical cutoff criteria for an internalizing disorder. For this objective, adolescents were grouped into those who met clinical cutoff scores for internalizing problems at both FU1 and FU2 (hereafter “Middle Onset”), and who met clinical cutoff scores for internalizing problems at FU2 only (hereafter “Late Onset”). Three fMRI tasks were examined: Faces Task, Stop Signal Task, and Modified Incentive Delay Task (see Appendix 1 for description of all measures and tasks). Select regions of interest were chosen to examine based on existing literature.

For the Faces Task, the amygdala and hippocampus were examined, as they are limbic regions involved in the memory and regulation of emotion; further, they are regions that have been associated with youth depression and anxiety in both structural and functional studies [72, 98, 99]. As reviewed, there is mixed evidence regarding hippocampal activation and volume in adolescents with depression and anxiety; reviews of neuroimaging findings in youth and adolescents illustrate that several studies have shown reduced volume, but less evidence exists for clear activation differences in emotional tasks [72, 98, 99]. Therefore, it was hypothesized that there will be group differences in hippocampal volumes at both Baseline and FU2, such that adolescents in the Middle Onset group, compared with the Late Onset and control groups, will demonstrate reduced hippocampal volumes and increased hippocampal activation during fearful faces on an emotional faces task. With regard to the amygdala, reviews of neuroimaging findings in youth and adolescents with internalizing symptoms [72, 98, 99] have demonstrated increased amygdala activation while viewing fearful and emotional faces and rating memory of emotional faces. Volumetric differences appear to be mixed,

with some studies showing decreased volume and some showing no differences. Therefore, based on current literature, it was hypothesized that amygdala volume will be significantly decreased, and activation will be significantly increased, during emotion processing (i.e., viewing anger during the Faces Task) for the Middle and Late Onset groups compared with controls. These differences were expected to be found at both Baseline and FU2.

For the Stop Signal Task (SST), seven bilateral ROIs were examined: 1) dorsolateral superior frontal gyrus, 2) superior frontal gyrus, orbital part, 3) middle frontal gyrus, 4) middle frontal gyrus, orbital part, 5) inferior frontal gyrus, opercular part, 6) inferior frontal gyrus, triangular part, and 7) inferior frontal gyrus, orbital part. These regions were chosen based on existing literature examining response inhibition using the SST that has found evidence for activity in the superior frontal gyrus, right inferior frontal gyrus and bilateral IFG, and in the middle frontal gyrus [100]. The IFG is thought to play an important role in emotion regulation and attention [101, 102]. Studies have previously found behavioral markers of “excessive response inhibition” in anxious individuals [103] and a positive relationship between depressive symptoms and the inferior frontal gyrus during response inhibition tasks [104]. With regard to volumetric differences, there is evidence of decreased GMV in the precentral gyrus and the superior frontal gyrus in adults with Generalized Anxiety Disorder [105], as well as decreased dorsolateral and dorsomedial prefrontal cortices [106]. Therefore, it is hypothesized that both the Middle and Late Onset groups will show significantly increased activity in these areas compared with controls. No hypotheses were made for volumetric differences.

For the MID Task, bilateral putamen and caudate were examined for two contrasts: Reward Outcome and Reward Anticipation. Some studies have found that individuals with Major Depressive Disorder exhibit weaker responses in the bilateral caudate during reward outcomes and in the putamen during reward anticipation [107] and reward outcome [108]. With regard to anxiety, the literature is somewhat more mixed. Adolescents with Social Anxiety have been found to exhibit hypersensitivity in the caudate and putamen when anticipating incentives, compared with those with generalized anxiety disorder and healthy controls [109], whereas those with Panic Disorder have showed reduced bilateral ventral striatal activation during reward anticipation [110]. With regard to volumetric differences in these regions, reduced GMV in the bilateral caudate has been found in women with depression [111]. A positive relationship between worry severity in individuals with Generalized Anxiety Disorder and GMV has been found in the left caudate and right putamen [112]. Based on this mixed evidence, it was hypothesized that the Middle and Late Onset groups would differ from the control group in that they would exhibit increased activation in the caudate and putamen during reward anticipation.

CHAPTER 2: METHOD

2.1. Participants

The High Internalizing (HI) participants will include adolescents from the IMAGEN study [10] who: a) have complete data on the Developmental And Well Being Assessment (DAWBA) self-report interview at Baseline, FU1, and FU2, and b) demonstrate higher degrees of internalizing symptomatology at FU2, defined by scoring a four or five on one of the six DAWBA band scores at FU2 (see full explanation of DAWBA interview and band scores in ‘Measures’). The HI group includes 91 adolescents (63 females and 28 males). The control group includes 1,244 participants (643 females and 601 males) who scored zero to three on the DAWBA band scores, therefore demonstrating varied subthreshold symptomatology, resulting in a total of 1,335 adolescents. Participants will be included in the HI group if they score a DAWBA band score of at least a four on Specific Phobia, Social Anxiety Disorder, Panic Disorder, Agoraphobia, Generalized Anxiety Disorder, or Depression. Sixty-seven individuals met DAWBA band score clinical cutoff criteria (greater than or equal to four) for a single internalizing disorder, 18 presented with two comorbid disorders, five presented with three comorbid disorders, and one presented with four comorbid disorders (see Table 1). See Table 2 for a breakdown of High Internalizing status by time point. Although the DSM-IV-TR includes Obsessive–Compulsive Disorder (OCD) and Posttraumatic Stress Disorder (PTSD) in the anxiety disorders category, there is evidence that these disorders have partly distinct etiologic underpinnings [113, 114]. Thus, this study does not include participants who met criteria for OCD and PTSD, consistent with the DSM-5 taxonomy for anxiety disorders [61]. DAWBA band scores have been shown to provide an

alternative to clinician-rated diagnoses, and are recommended for use particularly when studying associations with risk factors [115].

2.2. Procedure

Data were drawn from the IMAGEN study [10]. IMAGEN utilizes a multi-site, multidisciplinary design that is aimed at identifying both genetic and neurobiological bases of individual variability in psychological traits, and includes functional and structural neuroimaging data, behavioral, neuropsychological and genetic data for approximately 2,000 14-year-olds (Baseline), with follow up assessments at ages 16 (FU1) and 18-19 (FU2). Participants were from eight European sites. Ethics committees approved the study at each participating site. After study personnel described the IMAGEN study to participants and their parents, written informed consent was obtained. Data were collected from participants by both home assessments and by study center visits. Data obtained from participants included imaging of brain structure and brain activity; cognitive and behavioral assessments; self-report questionnaires using a number of psychosocial measures looking at factors such as relationships, feelings, and personality; questionnaires related to drug and alcohol use; and blood sampling for genetic and biological analyses. Full procedural information can be found in the online Standard Operating Procedures (<https://imagen-europe.com>).

2.3. Measures

Multiple measures were included in analysis for the current study (see <https://imagen-europe.com/> for complete list of all IMAGEN measures).

2.3.1. Psychopathology

Psychopathology was determined by the *Developmental and Well-Being Assessment* [116], a package of computer-administered interviews, questionnaires, and rating techniques that generates ICD-10 and DSM-IV psychiatric diagnoses for youth. Although the DAWBA obtains both adolescent- and parent-report, adolescent self-report was used for the current study. Adolescent self-report of internalizing psychopathology has been shown to be more accurate than parental report of the same symptoms, based on the nature of the symptoms of anxiety and depression [117]. Based on adolescent responses, a computer algorithm generates scores predicting the likelihood of meeting criteria for ICD-10 or DSM-IV diagnoses; these are defined as probability “band scores.” Six probability bands indicate the likelihood that an individual meets criteria for a disorder, ranging from a probability of <0.1% to a probability of >70% of having the relevant diagnosis. The outcome variable in the current study is defined as a score of four or a five on one of the six DAWBA band scores at FU2. Only adolescent, and not parent, reports will be used for the proposed study. Change scores in maximum DAWBA band score from Baseline to FU1 will also be included in the analysis as predictor variables. Although the DAWBA has largely been utilized in epidemiological, as opposed to clinically-applied, studies, DAWBA band scores have been shown to yield prevalence estimates that broadly compare to clinician-rated diagnoses [115]. Questions regarding whether adolescents had engaged in psychotherapy and/or had been prescribed psychiatric medication were not included in the IMAGEN assessment battery; therefore, this information was not able to be included in the current study.

2.3.2. Temperament

Temperament was assessed using the Temperament and Character Inventory–Revised (TCI-R) [118]. The Novelty-Seeking scale from the TCI-R was administered to assess trait dimensions specifically related to disinhibitory psychopathology. Thirty-four items, each with a five-point Likert scale, were administered to adolescents about themselves and to parents about themselves. Summary variables include exploratory excitability vs. stoic rigidity, impulsiveness vs. reflection, extravagance vs. reserve, disorderliness vs. regimentation, and novelty seeking. Sum scores were used. Both adolescent and parent reports will be included.

2.3.3. Personality

Personality was assessed using the NEO Personality Inventory-Revised (NEO-PI-R) [119]. The NEO PI-R consists of 240 questions intended to measure the Big Five Personality Traits, and assesses personality based on the Five-Factor Model of personality. Both mean and sum scores for Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Openness to Experience will be used. Both adolescent and parent reports will be included.

2.3.4. Substance Use

Substance Use was assessed using two measures. The first measure is the Substance Use Risk Profile Scale (SURPS) [120]. The SURPS consists of 23 questions intended to assess levels of several personality risk factors for substance abuse/dependence and psychopathology, including hopelessness, anxiety sensitivity, impulsivity, and sensation seeking. The instrument is valuable in assessing impulsivity and sensation seeking, and has been shown to have good test-retest reliability and

convergent and discriminate validity. Adolescent-reported mean scores for Anxiety Sensitivity, Negative Thinking, Impulsivity, and Sensation Seeking will be used. The second measure is the European School Survey Project on Alcohol and Drugs (ESPAD) [121]. The ESPAD assesses substance use and is part of an international study on substance use among European students. The ESPAD category scores are as follows (Score(Lifetime occurrences)): 0(0), 1(1-2), 2(3-5), 3 (6-9), 4(10-19), 5(20-39), 6(40 or more). Both adolescent and parent reports will be used.

2.3.5. Puberty

Puberty was assessed using the Puberty Development Scale (PDS) [122]. The PDS is an eight-item self-report measure that assesses the pubertal status of participants in the IMAGEN study. The PDS assesses physical development (based on Tanner stages) with separate forms for males and females. There are five categories of pubertal status: prepubertal, beginning pubertal, midpubertal, advanced pubertal, postpubertal. Participants answered questions about their growth in stature and pubic hair. Puberty stage score was used. Adolescent report was used.

2.3.6. Family and Life Events

Parental conflict was assessed using the Conflict Tactics Scale (CTS2) [123]. The CTS2 is a 78-item instrument that is completed by parents about parents, and is widely used to assess and measure domestic violence against a partner in a relationship. The CTS2 scales measure victimization and perpetration by assessing for three tactics often used in conflicts between partners: Physical Assault, Psychological Aggression, and Negotiation. Additionally, there are scales to measure injury and sexual coercion of and/or by a partner. Mean scores for Physical Assault, Injury, Psychological Aggression,

Negotiation, and Sexual Coercion were used. Life events were measured by the Life-Events Questionnaire (LEQ) [124]. The LEQ includes 39 items that measure the occurrence (e.g. ever, in the past year) and the perceived desirability of events covering the following domains: Family/Parents, Accident/Illness, Sexuality, Autonomy, Deviance, Relocation, and Distress. Mean lifetime frequency and Feeling Valence scores for Family/Parents events, Accident/ Illness events, Sexuality events, Autonomy Events, Deviance Events, Relocation events, and Distressing Events were used. Adolescent report was used.

2.3.7. Family History and Demographics

Family History was assessed using the Genetic Screening and Family History of Psychiatric Disorders Interview (GEN). The GEN assesses parent-reported family history information regarding the birth and ethnicity of the adolescents' parents and grandparents, as well as a history of psychopathology in first- and second-degree relatives.

2.3.8. Cognitive Functioning

Cognitive functioning was assessed using a version of the Wechsler Intelligence Scale for Children- Short Form (WISC-IV; [125]. The version that was administered and included subtests Block Design, Matrix Reasoning, Similarities, and Vocabulary. Perceptual Reasoning and Verbal Comprehension indices were used.

2.3.9. Attention

Two tasks were used to examine attention during emotional stimuli; both were administered to adolescents. The first measure that assesses attention to emotions is the Emotional Faces Dot-Probe Task (DOT PROBE) [126]. The dot-probe task indexes

attentional bias for emotional stimuli. Two face stimuli appeared at each side of the screen followed by a probe behind one of the faces, and participants indicate which side the probe was on. Three emotions were used: happy, angry, and fear. This task captures information regarding attentional biases towards positive and negative facial expressions (i.e., socially reinforcing and punishing information), relative to neutral facial expressions. Reaction times and number of congruent and incongruent trials for angry, fear, and happy faces were used. The second measure is the Morphed Faces Task (IDENT) [127]. The IDENT uses stimuli from empirically valid and reliable pictures from the Facial Affect Series [128]. This series contains pictures of four facial expressions conveying different emotions (happiness, fear, sadness, and anger), which have previously demonstrated socially reinforcing/ punishing properties. The presentation of the expression, which morph from neutral to emotional, is continued either until the end of 20 frames, or until the participant indicates that s/he is sure of the emotion on five consecutive frames. Ability to recognize emotional expressions (i.e., latency to detect emotion) was used.

2.3.10. Risk-Taking

Risk-taking behavior was assessed by the Cambridge Gambling Task (CGT; [129]). Participants completed the CGT to assess risk-taking behavior. Each trial consists of red and blue boxes displayed on the screen, and the participant must guess whether a yellow token is hidden in a blue or red box. Participants begin with a number of points and can select points to gamble on their judgment. Participants try to accrue as many points as possible. Delay aversion, deliberation time, overall proportion bet, quality of decision-making, risk adjustment, and risk-taking variables was used.

2.3.11. Functional and Structural MRI

There are three fMRI tasks in the IMAGEN study. First, the Stop Signal Task (SST) was used to assess motor response inhibition. The SST required participants to respond to regularly-presented visual Go stimuli (e.g., arrows pointing left or right) but to withhold their motor response when the Go stimulus was followed unpredictably by a Stop signal (e.g., an arrow pointing upwards). Contrast images for successful inhibitions (“Stop Success”) and unsuccessful inhibitions (“Stop Failure”) were used. Second, the Modified Incentive Delay (MID) task was used to assess reward processing. The MID task required participants to use button presses to respond to the location of targets presented on the monitor. Participants indicated whether the target appeared on the left or right side of the monitor display as quickly as possible. If the participants responded while the target was on the screen, points were received; if they responded before the target appeared, or after the offset of the target, they received zero points. A cue preceded the onset of each trial, indicating the position of the target and the number of points awarded for a successful response. A triangle indicated no points (“No Win”), a circle with one line indicated two points (“Small Win”), and a circle with three lines indicated ten points (“Big Win”). Contrast images for the anticipation period of Big Win - No Win (i.e., Reward Anticipation) and the outcome period for Big Win - No Win (i.e., Reward Feedback) was used. Third, the Face Task was used to assess face processing. This task required participants to passively view video clips displaying either ambiguous (i.e., neutral) or angry face expressions or control stimuli. Each trial consisted of short (2-5 seconds) black-and-white video clips depicting either a face in movement or a control stimulus. The task included a total of 19 stimuli blocks: 10 faces (angry or neutral) and 9

controls. Contrast images were calculated by subtracting ambiguous faces from angry faces. Contrasts included Neutral-Control, Angry-Control, and Angry-Neutral.

Structural MRI was also obtained. Brain data were parcellated into 278 regions of interest (ROIs) [130] and included regional and total grey matter volumes. In total, approximately 2,400 variables will be included in the prediction analysis. For the between-groups comparisons conducted for Objective 2, ROIs were derived from the automated anatomical labeling (AAL) atlas [131].

2.4. Data Analyses

2.4.1. Objective 1: Multimodal Risk Profiles

A logistic cross-validation regression analysis was conducted to calculate the probability that a 14-year-old would develop clinically-significant internalizing symptoms (i.e., HI group) by FU2 (age 18-19). A DAWBA band score of four or five at FU2 was the outcome variable. Adolescents with band scores of zero, one, two, or three at Bsl, FU1, and FU2 were identified as controls. Individuals in the control group had a range of internalizing symptom levels but did not meet clinical HI criteria. Cases and controls were not matched on any variables due to the nature of the analysis. The HI group included 91 adolescents and the control group included 1,244 adolescents.

Logistic regression was conducted, using the HI group status as the dependent variable. The logistic regression used elastic net regularization and ten-fold nested cross-validation. The data were first split into ten groups (hereafter “folds”). One fold (10% of the data) was set aside as independent testing data, and the remaining nine folds (90% of the data) were used as the training dataset to develop the regression model (i.e., identify the predictor variables and the optimal tuning parameters).

To identify the predictor variables and optimal tuning parameters, the remaining 90 percent of the data was split into 10 even folds (referred to hereafter as subfolds). One subfold was again set aside as an independent test set. The remaining nine subfolds (90% of the 81% of the data) were used to determine an optimal predictive elastic net regression model. The purpose of these subfold (i.e., “nested”) analyses was to tune the elastic net parameters and to identify the most generalizable model, as determined by performing best on the set aside subfold.

The elastic net regression reduces model overfitting through two regularization techniques, ridge and lasso regression, which use complementary strategies to minimize overfitting. These regularization techniques are considered useful for analyses with a large number of highly intercorrelated predictors [132]. Elastic net regression model includes two distinct parameters beyond standard regression, which have an unknown optimal level for controlling overfitting: alpha (α) and lambda (λ). α controls the ratio at which lasso versus ridge regression is used, while λ indicates the overall magnitude of regularization that occurs. Ten potential values of α , linearly spaced between .01 and 1, and 100 values of λ , logarithmically spaced between .001 and 1, were evaluated in order to determine the optimal combination of these parameters. The optimal parameter combination was identified based on which combination of α and λ best predicted the HI group status (the dependent variable) in the set-aside testing subfold (9% of the data), that is, which model returned the highest AUC for the logistic regression. Once the optimal model was identified in the training dataset, it was tested on the outer fold (i.e., the 10% of the data that were set aside at the outset).

This process was repeated ten times, with each subfold serving as the testing data once. Finally, this entire process was repeated 100 times and the mean AUC values across all 100 runs were recorded. Variables that survived at least eight of the ten folds across all 100 runs using the optimal model were reported. See Appendix 2 for visual representation of the analytic procedure. In summary, the reason for this cross-validation approach is to build a model with maximum generalizability by finding the model that best predicts the dependent variable in a distinct sample from the one on which it was trained, no matter which subjects were assigned to the training and testing sets (methodology adapted from Hudson et al., *in preparation*).

2.4.2. Objective 2: Between-group Comparisons

Repeated measures between-group comparisons of select regions of interest (ROIs) at Baseline and FU2 were conducted on three groups of adolescents: 1) adolescents from the control group who did not meet clinical cutoff scores for internalizing problems at any point in the study ($N=1,244$), 2) adolescents from the HI group who met clinical cutoff scores for internalizing problems at both FU1 and FU2 (“Middle Onset,” $N=32$), and 3) adolescents from the HI group who met clinical cutoff scores for internalizing problems at FU2 only (“Late Onset,” $N=51$). Both task activation and grey matter volume were examined using repeated measures analysis of covariance (ANCOVAs) in IBM SPSS Statistics for Macintosh, Version 24.0 and 25.0 to assess brain differences based on age of endorsing clinical cutoff criteria for internalizing disorders. The between-subjects factor was group status (*e.g.*, Controls, Middle Onset, Late Onset), and the within-subjects factor was time, with two levels: Baseline and FU2. Sex and site were included as nuisance covariates. Regions of interest were drawn from

the AAL atlas and both activation and structure were compared. Only individuals who had complete neuroimaging data at Baseline and FU2 on each task were used. Prior to running ANCOVAs, descriptive analyses were conducted, and indicated that the Middle Onset group had larger variance than the Control and Late Onset groups; therefore, Middle Onset group outliers were identified using stem-and-leaf plots in SPSS and were removed if they were deemed to be an extreme value. No more than three participants were excluded from each ROI examined. Within each ANCOVA, Bonferroni correction was used to control for multiple comparisons. After ANCOVAs were conducted, each p value was subjected to False Discovery Rate (FDR) controlling procedures to further correct for multiple comparisons. These were calculated using the MULTTEST procedure in SAS. Results are only reported for ANCOVAs that survived FDR-controlling procedures.

CHAPTER 3: RESULTS

3.1. Objective 1: High Internalizing (HI) Group Prediction

A k-fold cross-validated logistic regression analyses using elastic net regularization was used to calculate the probability that a 14-year-old would develop clinically-significant internalizing symptomatology by FU2. The mean area under the ROC curve was 0.78, $p < .0001$. Thirteen variables predicted clinical group status at FU2 (see Table 3 and Figure 1 for predictors). Predictors included higher psychopathology levels at Baseline (i.e., Agoraphobia) and FU1 (i.e., Depression, Social Anxiety, Agoraphobia, summed psychopathology score); parent personality measured at Baseline (i.e., parental Neuroticism); adolescent personality measured at Baseline (i.e., Neuroticism) and FU1 (i.e., Negative Thinking, Neuroticism, Impulsivity); higher lifetime frequency of adolescents' stressful life events (i.e., Distressing Events); and increased activation in the left dorsolateral prefrontal cortex (Brodmann Area 9) and the left parietal lobe (Brodmann area 7) during successful inhibition on the SST. *Post-hoc* regressions indicated that each of these variables, when tested in isolation, significantly predicted clinical group status except for parental Neuroticism at Baseline.

3.2. Objective 2: Between-group Comparisons

3.2.1. Faces Task

With regard to group differences in region-specific activation during the Faces task, bilateral hippocampus, parahippocampus, and amygdala were compared between Control, Middle Onset, and Late Onset groups for three contrasts: neutral-control, angry-control, and angry-neutral. Each ROI was tested separately. For the neutral-control contrast, adolescents with complete data at both Baseline and FU2 yielded the following

participants in each group: Controls ($N=1039$), Middle ($N=27$), Late ($N=42$). For this contrast, there were no main effects of Group or Group x Time interactions in any ROIs. However, many ROIs showed a main effect of Time, with most showing a decrease. ROIs with main effects of time demonstrating a decrease included the left hippocampus, $F(1, 1097)=16.31, p<.001$, (Baseline $M=0.12, SD=0.02$; Follow-Up 2 $M=0.07, SD=0.02$); right hippocampus, $F(1, 1097)=9.09, p<.01$, (Baseline $M=0.16, SD=0.02$; Follow-Up 2 $M=0.14, SD=0.02$); left parahippocampus, $F(1, 1097)=19.32, p<.001$, (Baseline $M=-0.014, SD=0.02$; Follow-Up 2 $M=-0.099, SD=0.02$); right parahippocampus, $F(1, 1097)=8.57, p<.01$, (Baseline $M=0.02, SD=0.02$; Follow-Up 2 $M=-0.04, SD=0.02$); and left amygdala, $F(1, 1097)=11.69, p<.01$, (Baseline $M=0.26, SD=0.03$; Follow-Up 2 $M=-0.21, SD=0.03$). See Figure 2 for results.

For the angry-control contrast, there was a significant main effect of time for activation in the left amygdala, $F(1, 1095)=6.92, p<.01$, with overall activation levels increasing over time (Baseline $M=0.20, SD=0.03$; Follow-Up 2 $M=0.30, SD=0.03$). There were no significant effects of Time, Group, or Time x Group interactions in the other ANCOVAs. See Figure 3 for results.

For the angry-neutral contrast, there were no main effects of Group or Time x Group interactions in any ROIs; however, many ROIs showed a main effect of Time, with most showing an increase in activation over time. These included the left hippocampus, $F(1, 1095)=11.67, p<.01$, (Baseline $M=-0.02, SD=0.02$; Follow-Up 2 $M=0.07, SD=0.02$); right hippocampus, $F(1, 1095)=7.77, p<.05$, (Baseline $M=-0.01, SD=0.02$; Follow-Up 2 $M=0.03, SD=0.02$); left parahippocampus, $F(1, 1095)=9.84, p<.01$, (Baseline $M=0.02, SD=0.03$; Follow-Up 2 $M=0.12, SD=0.02$); and the left

amygdala, $F(1, 1095)=13.80$, $p<.001$, (Baseline $M=-0.09$, $SD=0.04$; Follow-Up 2 $M=0.09$, $SD=0.04$). See Figure 4 for results.

3.2.2. Stop Signal Task

For the Stop Signal Task, ANCOVAs were conducted to examine bilateral activation in the following regions of interest: 1) dorsolateral superior frontal gyrus, 2) superior frontal gyrus, orbital part, 3) middle frontal gyrus, 4) middle frontal gyrus, orbital part, 5) inferior frontal gyrus, opercular part, 6) inferior frontal gyrus, triangular part, and 7) inferior frontal gyrus, orbital part. Each bilateral region was compared between Control, Middle Onset, and Late Onset groups for two contrasts: Stop Success and Stop Failure. Adolescents with complete data at both Baseline and FU2 yielded the following participants in each group: Controls ($N=1,052$), Middle Onset ($N=25$), Late Onset ($N=42$). Results are reported for ANCOVAs that survived False Discovery Rate controlling procedures. Stop Success was examined first. There was one significant main effect of Group for the left inferior frontal gyrus, triangular part, $F(2,1108)=8.64$, $p<.001$, with participants in the Middle Onset group ($M=0.50$, $SD=0.09$) showing significantly increased activation levels than participants in the Control group ($M=0.18$, $SD=0.01$). There were no Time x Group interactions in any ROIs; however, many ROIs showed a main effect of Time, with all showing a decrease in activation over time. These included the left superior frontal gyrus, orbital part, $F(1, 1105)=7.70$, $p<.01$, (Baseline $M=0.23$, $SD=0.06$; Follow-Up 2 $M=0.10$, $SD=0.05$); the right superior frontal gyrus, orbital part, $F(1, 1106)=4.86$, $p<.05$, (Baseline $M=0.27$, $SD=0.06$; Follow-Up 2 $M=0.17$, $SD=0.05$); the right inferior frontal gyrus, opercular part, $F(1, 1108)=11.31$, $p<.01$, (Baseline $M=0.96$, $SD=0.05$; Follow-Up 2 $M=0.74$, $SD=0.05$); and the right inferior frontal gyrus,

triangular part, $F(1,1108)=7.65, p<.05$, (Baseline $M=0.59, SD=0.05$; Follow-Up 2 $M=0.46, SD=0.04$). No other ANCOVAs were significant. See Figure 5 for results.

Activation differences in the Stop Signal Task during Stop Failure were then examined. There were no significant main effects of Group or Group x Time interactions; however, there were four ROIs that showed a main effect of Time, with all showing a decrease in activation over time. These included the left superior frontal gyrus, orbital part, $F(1,1108)=5.11, p<.05$, (Baseline $M=0.25, SD=0.06$; Follow-Up 2 $M=0.05, SD=0.05$); the left middle frontal gyrus, orbital part, $F(1,1108)=5.97, p<.05$, (Baseline $M=0.26, SD=0.08$; Follow-Up 2 $M=0.05, SD=0.06$); the right inferior frontal gyrus, opercular part, $F(1,1108)=6.32, p<.05$, (Baseline $M=0.90, SD=0.06$; Follow-Up 2 $M=0.75, SD=0.05$); and the right inferior frontal gyrus, triangular part, $F(1,1108)=5.51, p<.05$, (Baseline $M=0.48, SD=0.05$; Follow-Up 2 $M=0.36, SD=0.05$). See Figure 6 for results.

3.2.3. Modified Incentive Delay Task

To assess potential activation differences over time or by group status in the Modified Incentive Delay (MID) task during both Reward Anticipation and Reward Outcome, ANCOVAs were conducted examining bilateral caudate and putamen at Baseline and Follow Up 2. There were no significant effects of Time, Group, and/or Time x Group interactions for this task.

3.2.4. Gray Matter Volume: Faces Task Regions

Grey matter volume differences in the same brain regions that were compared on activation were also examined using ANCOVAs, with site and sex as covariates. All regions of interest were corrected for total GMV. Adolescents with complete data at both

Baseline and FU2 yielded the following participants in each group: Controls ($N=1109$), Middle ($N=27$), Late ($N=43$). First, ROIs assessed in the Faces task (bilateral hippocampus, parahippocampus, amygdala) were compared. There were no significant main effects of Group or Group x Time interactions; however, there was a main effect of Time for all ROIs, with GMV increasing slightly over time. These ROIs included the left hippocampus, $F(1,1168)=61.60$, $p<.0001$, (Baseline $M=0.0043$, $SD=0.000017$; Follow-Up 2 $M=0.0045$, $SD=0.000017$); right hippocampus, $F(1,1168)=60.61$, $p<.0001$, (Baseline $M=0.0038$, $SD=0.000016$; Follow-Up 2 $M=0.0041$, $SD=0.000016$); left parahippocampus, $F(1,1168)=94.64$, $p<.0001$, (Baseline $M=0.0052$, $SD=0.000002$; Follow-Up 2 $M=0.0054$, $SD=0.000002$); right parahippocampus, $F(1,1167)=71.35$, $p<.0001$, (Baseline $M=0.0065$, $SD=0.000002$; Follow-Up 2 $M=0.0068$, $SD=0.000002$); left amygdala, $F(1,1168)=115.10$, $p<.0001$, (Baseline $M=0.0013$, $SD=0.000005$; Follow-Up 2 $M=0.0014$, $SD=0.000005$); and the right amygdala, $F(1,1167)=34.49$, $p<.0001$, (Baseline $M=0.00146$, $SD=0.000006$; Follow-Up 2 $M=0.00153$, $SD=0.000005$). See Figure 7 for results.

3.2.5. Gray Matter Volume: Stop Signal Task Regions

For ROIs examined in the Stop Signal Task, there were no significant main effects of Group or Group x Time interactions; however, for several ROIs there was a main effect of Time, with all ROIs decreasing slightly over time. Regions that showed decreased GMV over time are reported first. There were significant main effects of time for the left dorsolateral superior frontal gyrus, $F(1,1168)=111.30$, $p<.0001$, (Baseline $M=0.0132$, $SD=0.000005$; Follow-Up 2 $M=0.0130$, $SD=0.000004$); the left middle frontal gyrus, $F(1,1168)=114.76$, $p<.0001$, (Baseline $M=0.020$, $SD=0.000006$; Follow-Up 2

$M=0.019$, $SD=0.00007$); the right middle frontal gyrus, $F(1,1168)=94.50$, $p<.0001$, (Baseline $M=0.021$, $SD=0.00007$; Follow-Up 2 $M=0.020$, $SD=0.00006$); the left inferior frontal gyrus, triangular part, $F(1,1168)=70.11$, $p<.0001$, (Baseline $M=0.0106$, $SD=0.00003$; Follow-Up 2 $M=0.0105$, $SD=0.00003$); and the right inferior frontal gyrus, triangular part, $F(1,1168)=404.95$, $p<.0001$, (Baseline $M=0.0078$, $SD=0.00003$; Follow-Up 2 $M=0.0076$, $SD=0.00003$). See Figure 8 for results.

3.2.6. Gray Matter Volume: Modified Incentive Delay Task Regions

There were no main effects of Group or Group x Time interactions in any ROIs. However, two ROIs showed a main effect of Time, with all showing a slight increase over time. These ROIs included the left caudate, $F(1,1168)=31.86$, $p<.0001$, (Baseline $M=0.0037$, $SD=0.00002$; Follow-Up 2 $M=0.0038$, $SD=0.00002$) and the right caudate, $F(1,1168)=77.81$, $p<.0001$, (Baseline $M=0.0038$, $SD=0.00002$; Follow-Up 2 $M=0.0039$, $SD=0.00002$). See Figure 9 for results.

CHAPTER 4: DISCUSSION

4.1. Objective 1: High-Internalizing (HI) Group Prediction Results

Thirteen variables from psychopathology, adolescent and parent personality, stressful life events, and functional MRI domains predicted High Internalizing symptoms in adolescents at FU2 (HI group). No genetic variables survived statistical threshold in this analysis. In the psychopathology domain, higher Agoraphobia symptoms at both Baseline and FU1 survived as significant predictors of the HI group, suggesting that a persistent fear or avoidance of places where escape is difficult was associated with greater internalizing symptomatology in late adolescence. Notably, Agoraphobia symptoms were the only class of anxiety symptoms to emerge as predictors at both age 14 and age 16, suggesting that the persistence of these symptoms throughout several years during middle adolescence may place teens at especially high risk for higher internalizing symptoms later on. Higher Depression and Social Anxiety levels at FU1 also emerged as significant predictors of the HI group, as did greater total internalizing symptomatology at FU1. Results are consistent with previous literature which has consistently shown that anxiety and depression commonly “cross-predict” from youth to adulthood [2] and often cluster together.

Both adolescent and parent personality characteristics were positively associated with HI group status. Parental Neuroticism at Baseline, (but not at FU1) was the only parent personality factor associated with HI group status, suggesting that parental features of Neuroticism in early adolescence may be especially powerful factors in adolescents’ development of internalizing symptomatology in late adolescence. This finding is consistent with previous literature illustrating that Neuroticism is a core dimension of

internalizing psychopathology [26] and that parenting styles and parental modeling have consistently been implicated in the development and maintenance of youth anxiety [133] and depression [54] in youth. Interestingly, recent findings from a children-of-twins study showed that the association between parental and adolescent Neuroticism appears to be environmental rather than genetic, providing evidence that there is direct environmental transmission from parents to their children [134]. Given that Neuroticism has been shown to relate strongly with a broad internalizing factor [26], our findings that adolescent Neuroticism at both Baseline and FU1 predicted HI group status confirms previous evidence that higher levels of this personality characteristic in both early and middle adolescence contributes to increased internalizing symptoms by late adolescence and beyond. In addition to Neuroticism, adolescent Negative Thinking and Impulsivity at FU1 also predicted HI group status, suggesting that adolescents who demonstrate increased negative cognitive styles and impulsive behaviors in middle adolescence may be especially prone to more internalizing symptomatology in late adolescence. Negative Thinking has been implicated as a transdiagnostic contributor to anxiety and mood disorders [135], and negative thinking styles are commonly seen in both depressive and anxiety disorders (e.g., worthlessness, catastrophizing, expecting the worst). While Impulsivity has generally been associated with externalizing disorders, such as Attention-Deficit / Hyperactivity Disorder, it has also been linked with internalizing symptoms. For example, Cosi and colleagues (2011) found that motor, but not cognitive, Impulsivity was positively associated with anxiety and depression in youth ages nine to thirteen [136].

Higher lifetime frequency of adolescents' Distress Events, as measured on the Life Events Questionnaire administered at FU1, was positively associated with HI group

status, suggesting that exhibiting more behaviors that signal distress or negative changes at middle adolescence (but not early) may be a particularly important indicator of increased internalizing symptoms by late adolescence. Examples of items that make up the Distress Events scale included gaining weight, running away from home, and getting poor grades. This finding is particularly important in the greater context of internalizing symptoms, which are often more difficult for caregivers and parents to detect than those related to externalizing disorders, such as ADHD or Oppositional Defiant Disorder. These behavioral markers of distress may be an important way for others to identify and distress and impairment related to internalizing problems in adolescents and intervene accordingly.

With regard to neurobiological variables, increased activation in the left dorsolateral prefrontal cortex (Brodmann Area 9) during successful response inhibition at Baseline was associated with HI group status at FU2, suggesting that adolescents who subsequently went on to develop clinically-impairing anxiety and depressive symptoms dedicated increased resources to an area typically involved with executive functioning and decision making compared with individuals who did not go on to experience high internalizing symptoms. Similarly, increased activation at Baseline in the left parietal lobe during successful response inhibition (Brodmann area 7) was positively associated with HI group status at FU2. As the parietal area has been shown to contribute to the inhibitory process [137], it appears that these adolescents may be utilizing greater resources when required to inhibit a response. Additionally, the parietal cortex is an area of great connectivity [138], and increased activation in the HI group suggests utilization of resources related to decision-making and information-processing during response

inhibition. To examine whether the HI group exhibited differences in stop-signal response time (SSRT) compared with Controls, *post-hoc* comparisons were conducted and yielded no significant difference in SSRT between the groups at Baseline or Follow-Up 2. This finding illustrates that, while there were no behavioral differences in adolescents' performance on the task, those with higher levels of internalizing symptoms appeared to allocate greater cognitive resources to the process of inhibiting a response compared with controls.

4.2. Objective 2: Between-Group Comparisons Results

Results of between-group comparisons on task activation showed several ROIs that changed over time, but did not yield group differences or Group x Time interactions, with one exception (left inferior frontal gyrus, triangular part during Stop Success on the SST). With regard to task activation on the Faces task, activation in the amygdala, hippocampus, and parahippocampus generally decreased over time for the neutral – control contrast, suggesting that adolescents' responses to neutral facial expressions decreased by late adolescence. In contrast, for the anger conditions, there was increased activation over time. For the Angry – Control contrast, there was increased activation over time in the left amygdala. Although there was not a significant Group effect or Group x Time interaction, visual examination of the data suggest that the Middle and Late Onset groups demonstrated a decreased response at Baseline, compared with Controls, but by FU2 all groups exhibited similar activation levels. Similarly, for the Angry – Neutral contrast, several ROIs showed increased activation over time. This finding is consistent with previous work showing that sensitivity to recognizing anger increases sharply during the transition from adolescence to adulthood [139]. Although

there were no significant group activation differences, visual examination of the data suggests that the Middle and Late Onset groups generally exhibited more of an increase in activation over time than did Controls. Surprisingly, there were no group differences or Group x Time interactions for the Faces Task, which was contrary to expectations based on literature suggesting that individuals with internalizing symptoms have demonstrated increased amygdala activation while viewing fearful and emotional faces [72, 99].

The Stop Signal Task was the only task that yielded an activation difference between groups. Specifically, adolescents in the Middle Onset group showed significantly increased activation during Stop Success (i.e., response inhibition) in the left inferior frontal gyrus, triangular part. This finding suggests that adolescents who presented with more persistent internalizing symptoms beginning in middle adolescence and continuing through late adolescence utilized greater resources when engaging in response inhibition. This finding was particularly interesting given the results of Objective 1, in that a pattern of increased STOP-related activation during successful response inhibition emerged for adolescents who ultimately developed HI symptoms in late adolescence. Although significant research points to the role of the right inferior frontal gyrus in response inhibition, there is also evidence to suggest that the left inferior frontal gyrus plays a critical role in successfully implementing inhibitory control over motor processes [140]. Thus, adolescents with persistent symptomatology may allocate greater resources to both the cognitive and motor tasks associated with inhibiting responses. The remainder of the ROIs also showed decreases in activation over time for response inhibition, suggesting that all three groups tended to utilize fewer neural resources when engaging in response inhibition later in adolescence at ages 18-19. While

no main effects of Group or Group x Time interaction remained significant after FDR-controlling procedures, visual examination of the data illustrates that the Middle Onset group consistently tended to exhibit different activation patterns than the other two groups. This difference was especially pronounced at Baseline, as the Middle Onset group exhibited greater activation than the control and Late Onset groups for all significant ANCOVAs. Activation decreases over time in four ROIs were also observed for the Stop Failure contrast, all four of which also showed significant decreases during Stop Success. This finding suggests that, regardless of whether response inhibition was successful or not, resources utilized in the process of inhibition tend to decrease from early to late adolescence. It is possible that this decrease in activation is associated with established patterns of cortical activation throughout adolescent development, in which activity becomes more focal and is related to enhanced cognitive performance [141]. Similar to Stop Success, visual examination of the data illustrate that the Middle Onset group had the highest activation levels at Baseline in all four ROIs (See Figures 5 and 6).

Contrary to expectations, there were no significant Time, Group, or Time x Group effects in Reward Anticipation and Reward Feedback contrasts within the MID task. Given that previous studies have shown reward anticipation and processing differences based on various types of psychopathology, it is possible that there was too much inter-subject variability to detect significant differences in reward processing within the Middle Onset and Late Onset groups.

Results of gray matter volume comparisons generally showed a consistent trend of volumetric decreases over time across several ROIs, which is consistent with grey matter maturation changes that occur during adolescence as a result of myelination [142].

We also found very slight but statistically significant grey matter increases in the bilateral caudate. Although this finding was contrary to expectations, as GMV in this area is generally thought to decrease during adolescence, some evidence exists for volumetric decreases during the adolescent period [143], although results were gender-specific. Notably, although statistically significant, all of these increases were extremely small. It is possible that our results reflect this continued maturing of certain regions before gray matter loss occurs in late adolescence. Another potential explanation for these findings is that the assessment of cortical grey matter used in the current study (VBM) may be a less sensitive measure of age-related grey matter loss [144].

4.3. Limitations and Conclusions

The present study has a number of strengths. Specifically, we utilized a large, longitudinal study design while drawing from a broad range of neuroimaging, genetic, behavioral, psychosocial, cognitive, and demographic data, thus enhancing our understanding of possible etiological mechanisms that contribute to internalizing symptomatology over the critical period of adolescent development. Despite these strengths, several important considerations apply to this study. First, IMAGEN study participants were drawn from a largely homogenous European sample that was predominantly White. Therefore, there is reason for concern that these results may not generalize to adolescents with a variety of identities (e.g., racial, ethnic, cultural, gender and sexual identity). Additionally, several potential group differences in ROIs both functionally and structurally were examined, resulting in a large number of comparisons, which may increase the likelihood of Type I errors. To address this issue, stringent corrections for multiple testing were utilized. First, within each comparison, Bonferroni

corrections were utilized. Subsequently, all ANCOVAs were subjected to False Discovery Rate correcting procedures, which eliminated some previously-significant results. Although significant socio-emotional and psychopathological information was obtained from adolescents, the IMAGEN study did not include measurement of whether adolescents had received psychotherapy and/or were prescribed psychiatric medications throughout the three time points examined. Therefore, these variables were not able to be examined or controlled for in our analyses, which is considered a limitation in the context of examining levels of internalizing symptomatology throughout the adolescent period.

In conclusion, results indicate that factors from multiple domains characterize adolescents at risk for developing high levels of internalizing symptoms. Importantly, our findings suggest that there were features of brain functioning during successful response inhibition that were consistently associated with future impairment in addition to psychopathology levels throughout adolescence, personality factors, and life events. Therefore, our findings illustrate that brain functioning in parietal and frontal regions related as powerfully as other environmental and psychological domains to future clinical diagnosis. Further, adolescents with more persistent internalizing psychopathology throughout the middle and late adolescent periods appear to utilize greater neural resources when engaging in successful response inhibition. While results of this study did not support significant group differences in select regions of interest within a community sample of adolescents, findings confirm and extend previous evidence regarding the effect of time on brain activation and grey matter volume, such that activation and volume change throughout the adolescent developmental period. Taken together, findings suggest that, while there appear to be brain-related risk factors that are specific to future

clinically-diagnostic symptoms, the timing of symptom onset does not necessarily lead to clear differences in neural activation or grey matter volume. These findings suggest nuance within our understanding of neurobiological variation within internalizing disorders in community samples of adolescents.

Figures

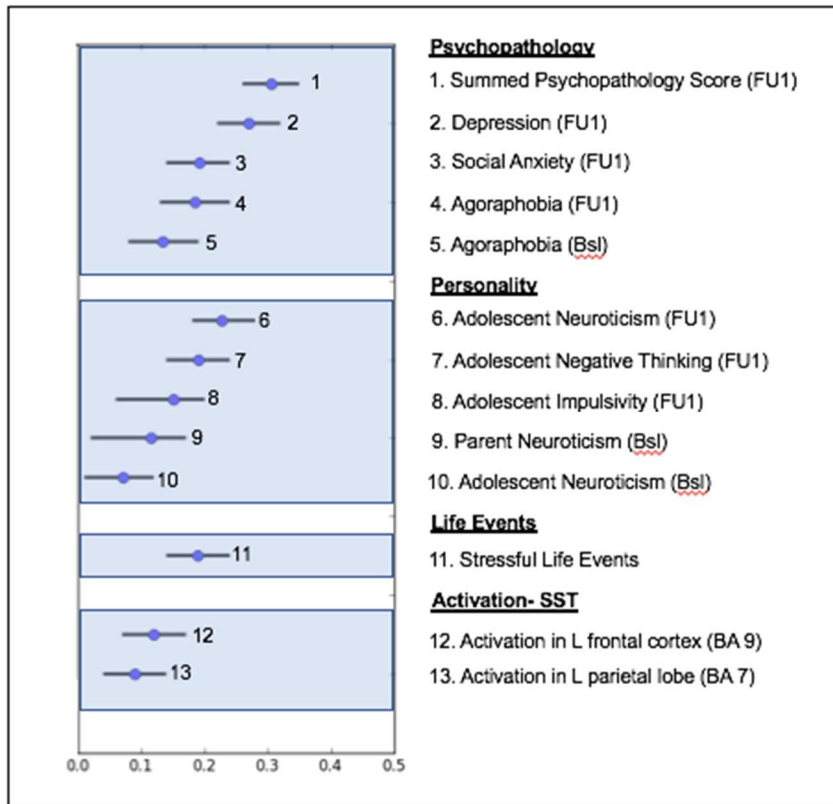


Figure 1. Point-biserial correlations (Pearson's r coefficients) between predictors from the k-fold cross-validated logistic regression and HI outcome.

Faces Task: Neutral - Control

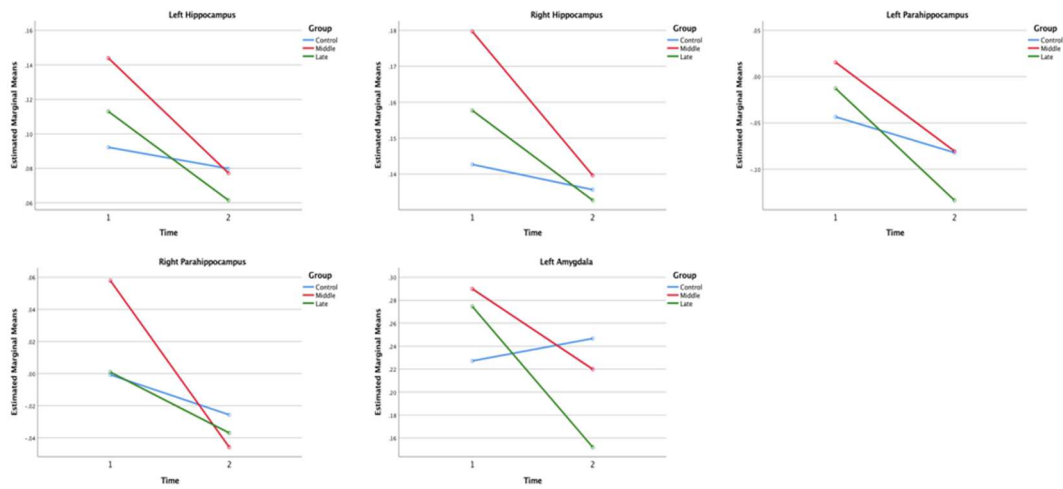


Figure 2: Faces Task, Neutral – Control contrast.

Faces Task: Angry - Control

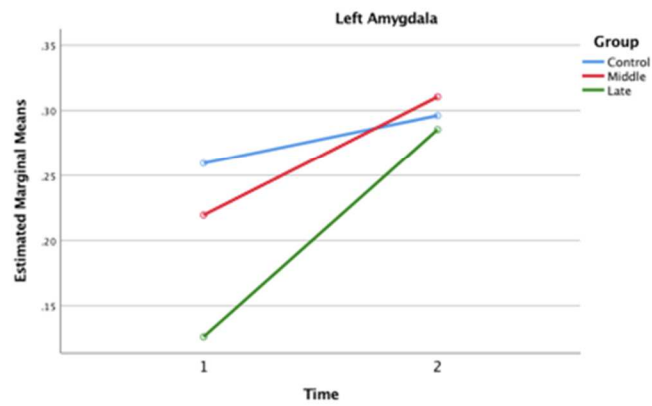


Figure 3: Faces Task, Angry – Control contrast.

Faces Task: Angry - Neutral

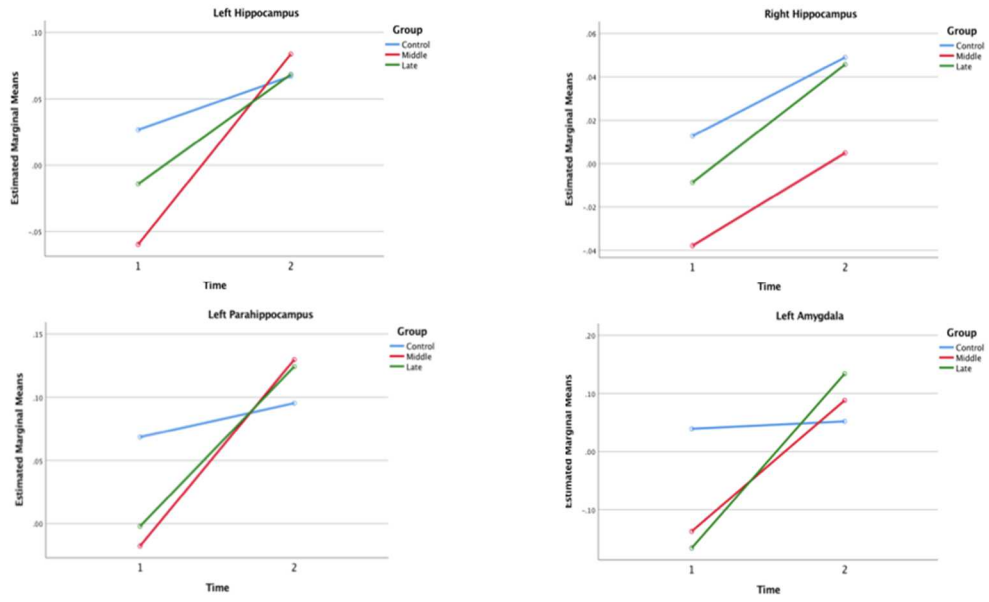


Figure 4: Faces Task, Angry – Neutral contrast.

Stop Signal Task: Stop Success

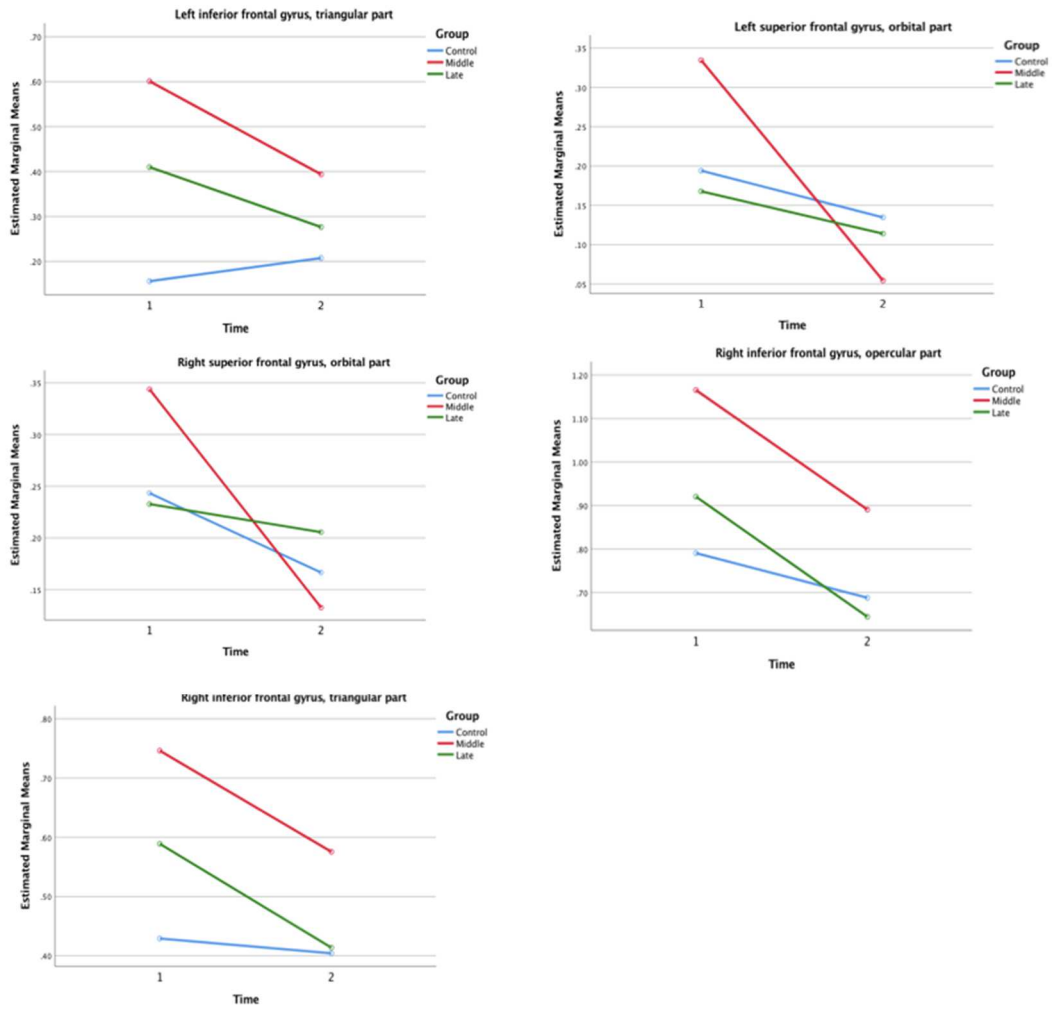


Figure 5: Stop Signal Task, Stop Success contrast.

Stop Signal Task: Stop Failure

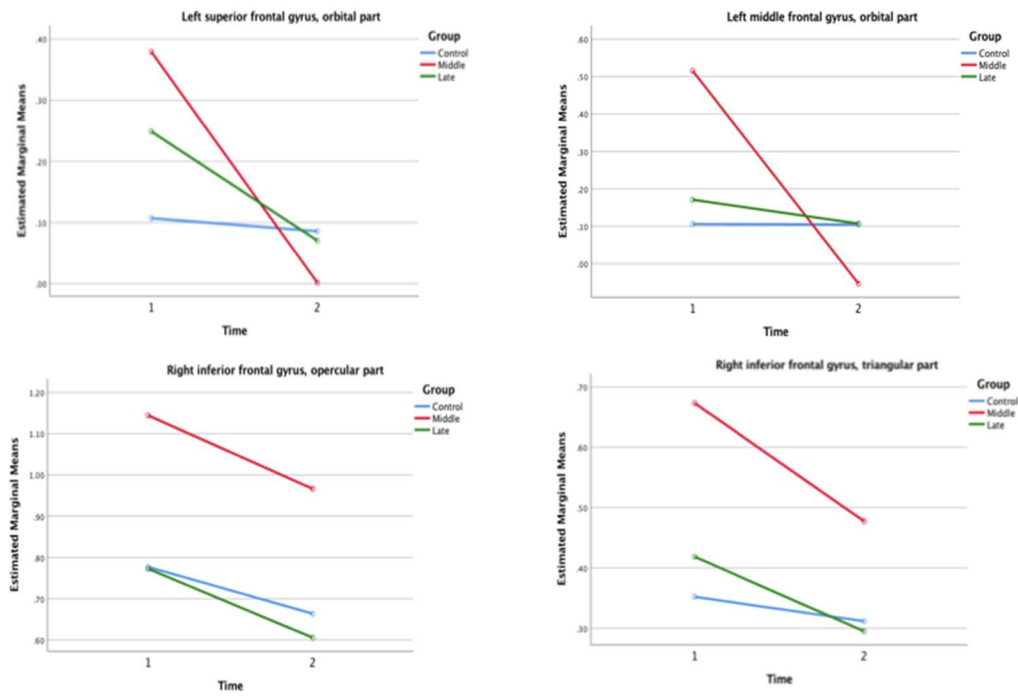


Figure 6: Stop Signal Task, Stop Failure contrast.

GMV: Faces Task Regions

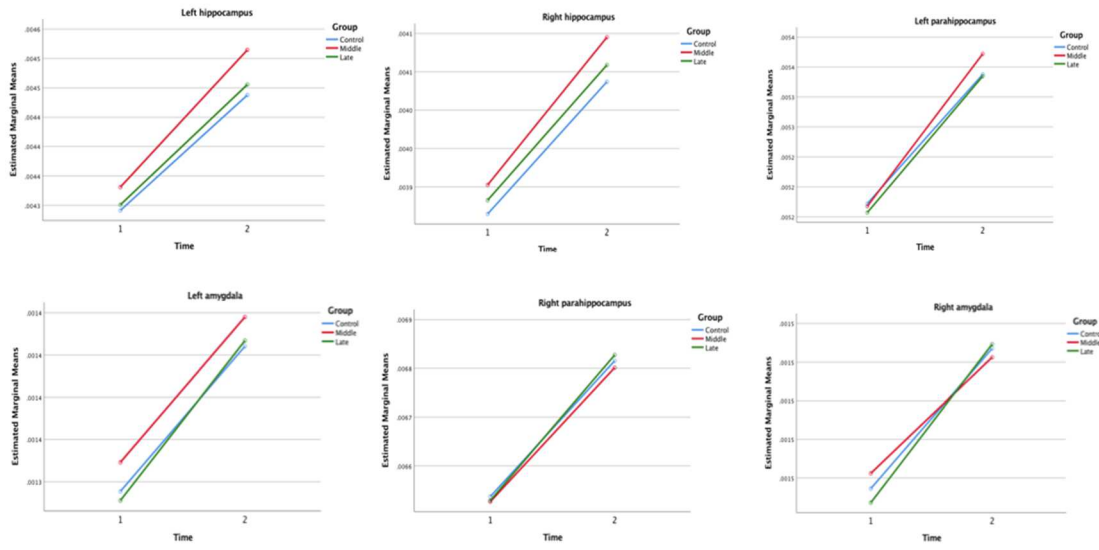


Figure 7: GMV, Faces Task ROIs.

GMV: Stop Signal Task Regions, Decreased Volume

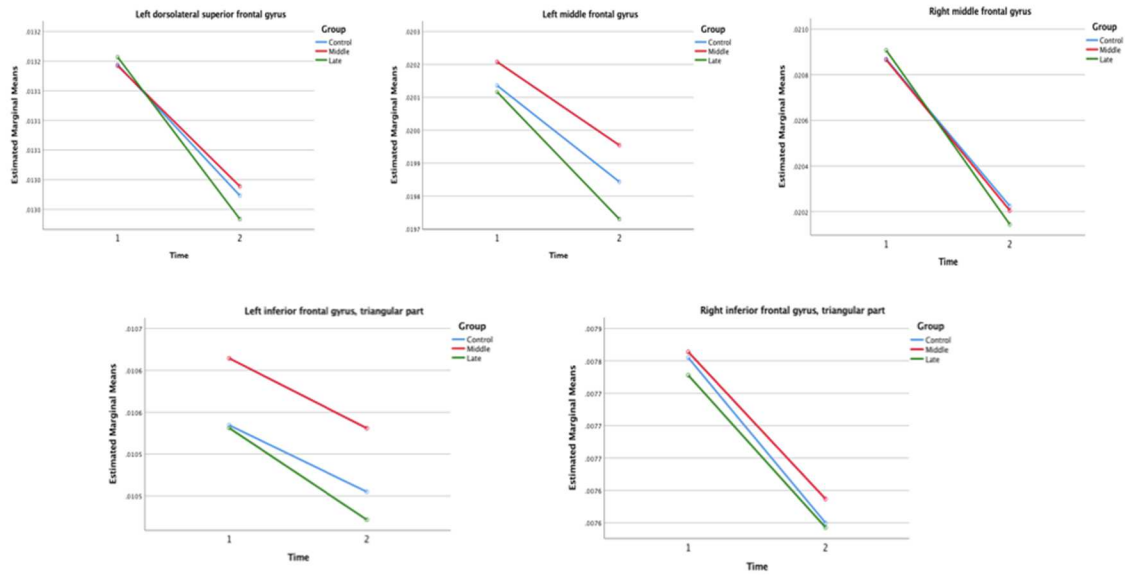


Figure 8: GMV, Stop Signal Task ROIs, Decreased Volume.

GMV: MID Task Regions

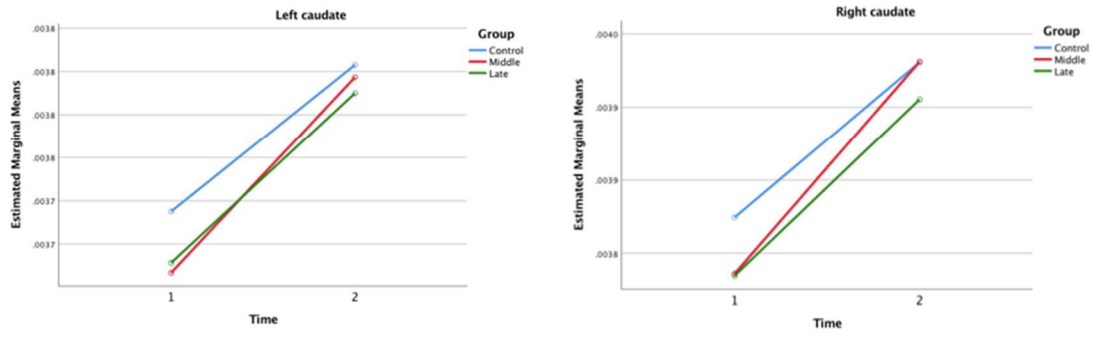


Figure 9: GMV, MID Task ROIs.

Tables

Table 1: Demographic and psychopathology variables among cases and controls.

	Cases	Controls
<i>Sex</i>		
Male	28	601
Female	63	643
<i>Psychopathology</i>		
Specific Phobia	5	
Social Anxiety	11	
Panic	4	
Agoraphobia	0	
Generalized Anxiety	9	
Depression	38	
Two comorbid diagnoses	18	
Three comorbid diagnoses	5	
Four comorbid diagnoses	1	

Table 2: Breakdown of High Internalizing status by time point.

Status at FU2	N
<i>HI at FU2</i>	
HI at FU2 only	51
HI at FU1 and FU2	32
<i>Non-HI by FU2</i>	
Never HI	1,244

Table 3: Predictors from k-fold cross-validated logistic regression. Predictors shown survived at least eight of the ten folds in all 100 runs of the k-fold cross-validated logistic regression. Positive beta weights indicate greater levels of the predictor in those with future diagnostic levels of internalizing problems. Mean $AUC = .78$, $SD = 0.01$, $p < .0001$. Bsl = Baseline, FU1 = Follow-Up 1.

Psychopathology (Mean β)	Life Events (Mean β)	Personality (Mean β)	Functional (Mean β)
Bsl Agoraphobia (0.06)	Distress Events (0.10)	Bsl Parental Neuroticism (0.04)	SST Stop Inhibition: left frontal cortex (0.05)
FU1 Depression (0.13)		Bsl Adolescent Neuroticism (0.10)	SST Stop Inhibition: left parietal lobe (0.04)
FU1 Social Anxiety (0.08)		FU1 Adolescent Neuroticism (0.09)	
FU1 Agoraphobia (0.06)		FU1 Adolescent Negative Thinking (0.09)	
FU1 Total Internalizing Symptoms (0.19)		FU1 Adolescent Impulsivity (0.05)	

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APPENDICES

Appendix 1. Description of all measures and tasks.

09

Measure	Summary Variables	Reporter		Bsl	FU1	FU2
		Adolescent	Parent			
<p>The Development and Well-Being Assessment Interview (DAWBA): The DAWBA is a package of interviews, questionnaires, and rating techniques designed to generate ICD-10 and DSM-IV psychiatric diagnoses for children and adolescents. Information from up to three sources (parents, adolescents, teachers) is obtained to generate probability bands that indicate the likelihood that an individual meets criteria for a DSM-IV disorder.</p>	<p>Specific Phobia, Social Anxiety, Panic, Agoraphobia, Generalized Anxiety, Other Anxiety, Major Depressive Disorders. Band scores will be used.</p>	X		X	X	X
<p>Temperament and Character Inventory – Revised (TCI-R): The Novelty-Seeking scale from the TCI-R was administered to assess trait dimensions specifically related to disinhibitory psychopathology. Thirty-four items, each with a five-point Likert scale, were administered.</p>	<p>Exploratory excitability vs. stoic rigidity, impulsiveness vs. reflection, extravagance vs. reserve, disorderliness vs. regimentation, novelty seeking. Sum scores will be used.</p>	X	X	X	X	
<p>NEO-PI-R (NEO): The NEO PI-R consists of 240 questions intended to measure the Big Five Personality Traits. The NEO-PI-R assesses personality</p>	<p>Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Openness to</p>	X	X	X	X	

based on the Five-Factor Model of personality.	Experience. Both mean and sum scores will be used.					
<p>Substance Use Risk Profile Scale (SURPS): The SURPS consists of 23 questions intended to assess levels of several personality risk factors for substance abuse/dependence and psychopathology, including hopelessness, anxiety sensitivity, impulsivity, and sensation seeking. The instrument is valuable in assessing impulsivity and sensation seeking, and has been shown to have good test-retest reliability and convergent and discriminate validity.</p>	Anxiety Sensitivity, Negative Thinking, Impulsivity, Sensation Seeking. Mean scores will be used.	X		X	X	
<p>European School Survey Project on Alcohol and Drugs (ESPAD): The ESPAD assesses substance use and is part of an international study on substance use among European students. The ESPAD category scores are as follows (Score(Lifetime occurrences)): 0(0), 1(1-2), 2(3-5), 3 (6-9), 4(10-19), 5(20-39), 6(40 or more). This measure was completed by adolescents about themselves and by parents about themselves.</p>	Parent marijuana use, adolescent tobacco use, adolescent alcohol use.	X	X	X	X	

<p>Puberty Development Scale (PDS): The PDS is an eight-item self-report measure that assesses the pubertal status of participants in the IMAGEN study. The PDS assesses physical development (based on Tanner stages) with separate forms for males and females. There are five categories of pubertal status: prepubertal, beginning pubertal, midpubertal, advanced pubertal, postpubertal. Participants answer questions about their growth in stature and pubic hair.</p>	Puberty stage	X		X		
<p>Conflict Tactics Scale (CTS2): The CTS2 is a 78-item instrument that is completed by parents, and is widely used to assess and measure domestic violence against a partner in a relationship. The CTS2 scales measure victimization and perpetration by assessing for three tactics often used in conflicts between partners: Physical Assault, Psychological Aggression, and Negotiation. Additionally, there are scales to measure injury and sexual coercion of and/or by a partner.</p>	Physical Assault, Injury, Psychological Aggression, Negotiation, and Sexual Coercion. Mean scores will be used.		X	X		
<p>Life-Events Questionnaire (LEQ): The LEQ includes 39 items that measure the occurrence (e.g. ever, in the past year) and the perceived desirability of events covering the following</p>	Family/Parents events, Accident/ Illness events, Sexuality events, Autonomy Events, Deviance Events, Relocation events, Distress	X		X	X	

domains: Family/Parents, Accident/Illness, Sexuality, Autonomy, Deviance, Relocation, and Distress.	Events. Mean lifetime frequency and Feeling Valence scores will be used.					
Genetic Screening and Family History of Psychiatric Disorders Interview (GEN): The GEN assesses family history information regarding the birth and ethnicity of the adolescents' parents and grandparents, as well as a history of psychopathology in first and second degree relatives.	Family race/ethnicity and family psychiatric history.	X	X	X		
Emotional Dot Probe (DOT PROBE): The dot-probe task indexes attentional bias for emotional stimuli. Two face stimuli appeared at each side of the screen followed by a probe behind one of the faces, and participants indicate which side the probe was on. Three emotions were used: happy, angry, and fear. This task captures information regarding attentional biases towards positive and negative facial expressions (i.e., socially reinforcing and punishing information), relative to neutral facial expressions.	Reaction times and number of congruent and incongruent trials for angry, fear, and happy faces.	X	X	X		
Morphed Faces Task (IDENT): The IDENT uses stimuli from the empirically valid and reliable pictures of the Facial Affect Series (Ekman and Friesen, 1976). This series contains pictures of four facial expressions	Latency to detect emotion.	X	X	X		

<p>conveying different emotions (happiness, fear, sadness, and anger), which have previously been demonstrated to have socially reinforcing/ punishing properties. The presentation of the expression, which morph from neutral to emotional, is continued either until the end of 20 frames, or until the participant indicates that s/he is sure of the emotion on five consecutive frames. Ability to recognize emotional expressions (i.e., latency to detect emotion) was recorded.</p>						
<p>Wechsler Intelligence Scale for Children- Short Form (WISC-IV): A version of the WISC-IV was administered and included subtests Block Design, Matrix Reasoning (to assess Perceptual Reasoning), Similarities, and Vocabulary (to assess Verbal Comprehension).</p>	<p>Perceptual Reasoning Index, Verbal Comprehension Index.</p>	<p>X</p>				
<p>Cambridge Gambling Task (CGT):. Participants completed the CGT to assess risk-taking behavior. Each trial consists of red and blue boxes displayed on the screen, and the participant must guess whether a yellow token is hidden in a blue or red box. Participants begin with a number of points and can select points to gamble on their judgment.</p>	<p>Delay aversion, deliberation time, overall proportion bet, quality of decision making, risk adjustment, and risk taking.</p>	<p>X</p>		<p>X</p>		

Participants try to accrue as many points as possible.						
<p>fMRI Face Task: The Face Task required participants to passively view video clips displaying either ambiguous (i.e., neutral) or angry face expressions or control stimuli. Each trial consisted of short (2-5 seconds) black-and-white video clips depicting either a face in movement or a control stimulus. The task included a total of 19 stimuli blocks: 10 faces (angry or neutral) and 9 control. Contrast images were calculated by subtracting ambiguous faces from angry faces.</p>	Contrasts to be used include Neutral-Control, Angry-Control, and Angry-Neutral.	X		X		X
<p>fMRI MID Task: The modified incentive delay (MID) task required participants to use button presses to respond to the location of targets presented on the monitor. Participants indicated whether the target appeared on the left or right side of the monitor display as quickly as possible. If the participants responded while the target was on the screen, points were received; if they responded before the target appeared, or after the offset of the target, they received zero points. A cue preceded the onset of each trial, indicating the position of the target and the number of points awarded for a</p>	Contrast images for the anticipation period of Big Win - No Win (i.e., Reward Anticipation) and the outcome period for Big Win - No Win (i.e., Reward Feedback).	X		X		X

successful response. A triangle indicated no points (“No Win”), a circle with one line indicated two points (“Small Win”), and a circle with three lines indicated ten points (“Big Win”).						
fMRI STOP Task The stop signal task required participants to respond to regularly presented visual Go stimuli (e.g., arrows pointing left or right) but to withhold their motor response when the Go stimulus was followed unpredictably by a Stop-signal (e.g., an arrow pointing upwards).	Contrast images for successful inhibitions (“Stop Success”) and unsuccessful inhibitions (“Stop Failure”) will be used.	X		X		X

Appendix 2. K-fold cross-validation analytic procedure.

