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Convergent neurobiological predictors of emergent psychopathology during adolescence

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Abstract

The adolescent brain undergoes significant structural and functional development. Through the use of magnetic resonance imaging in adolescents, it has been demonstrated that the prefrontal cortex, pertinent for executive control, demonstrates protracted development compared to limbic structures, active during emotion and reward processing. This asynchronous development creates a sensitive window during adolescence, in which many psychopathological disorders (i.e. mental health and substance use) emerge. This review outlines longitudinal studies that use magnetic resonance imaging to identify neurobiological predictors of emergent psychopathology (depression, anxiety and substance use), during adolescence. Studies identifying neurobiological markers that predict onset and escalation of these disorders, as well as those that predict successful treatment outcomes are explored. An emphasis is placed on frontolimbic brain structures, a convergent neurobiological target for both emergent mental health issues and emergent substance use. This knowledge is crucial, as it may be used to develop neurobiologically targeted prevention and intervention strategies for youth who are at-risk for developing these psychopathologies.

Introduction

Recent advances in longitudinal magnetic resonance imaging (MRI) have provided important insight into how the adolescent brain develops. Studies examining gray matter development have described both linear decreases and non-linear changes in cortical volume and thickness (Ostby et al., 2009; Paus, 2005; Shaw et al., 2008; Tamnes et al., 2010), as well as subcortical volume (e.g. amygdala, striatum, and hippocampus) (Ostby et al., 2009; Raznahan et al., 2014; Wierenga et al., 2014). Meanwhile, recent studies focusing on white matter development suggest linear increases and non-linear changes in volume and white matter microstructure (Lebel and Beaulieu, 2011; Ostby et al., 2009; Pfefferbaum et al., 2016; Simmonds et al., 2014) across adolescence. Importantly, it has been demonstrated that this development does not take place uniformly across the brain, but occurs in a region-specific manner (e.g. gray matter reaches earlier maturation in sensorimotor cortices compared to frontal and temporal cortices) (Gogtay et al., 2004). One area of increasing attention in adolescent neurodevelopment, is the apparent asynchronous development of the

prefrontal cortex and subcortical limbic structures. Studies have shown that the prefrontal cortex, a major component in executive control, demonstrates protracted development compared to limbic structures, active during emotion and reward processing (Mills et al., 2014; Simmonds et al., 2014). Together, continued development of gray and white matter during adolescence, and the asynchronous development of frontolimbic circuitry, creates what is now often referred to as a “sensitive period” during adolescent development (Fuhrmann et al., 2015).

Adolescence is a time during which there is an increased risk for developing psychopathology (i.e. anxiety and mood disorders) and substance use disorders, with half of all lifetime cases beginning by age 14 and three quarters by age 24 (Kessler et al., 2005). Recent data suggests that roughly 11% of adolescents (ages 13–18) have experienced a major depressive episode in their lifetime (Avenevoli et al., 2015), nearly one in three adolescents (32%) meet criteria for an anxiety disorder (Merikangas et al., 2010), and by 12th grade 42% of adolescents have experimented with alcohol and 33% with other illicit drugs (including marijuana) (Johnston et al., 2016). Furthermore, when investigating comorbidities between mental health disorders (including anxiety and depression) and substance use, it has been shown that prior diagnosis of a mental health disorder increases the risk for both initiating substance use, as well as transitioning from any use to problematic use (Conway et al., 2016). Recent reviews have suggested that underlying neurodevelopment, specifically the nonparallel development of frontolimbic circuitry, during this sensitive period in adolescence, may be driving both the emergence of mental health disorders (e.g. Swartz and Monk, 2014), as well as the initiation of substance use (e.g. Jordan and Andersen, 2017). This makes better understanding of the underlying neurobiological risk markers for emergent psychopathology and substance use during this time extremely relevant.

Neuroimaging can be used as a tool for understanding how clinical treatments (both pharmacological and behavioral) engage or modify underlying neurobiology (e.g. Feldstein Ewing et al., 2013). As our understanding of the underlying neurobiological mechanisms behind these intervention techniques grow, so does the necessity for a more complete knowledge of neurobiological targets for treatment. Along these same lines, if neurobiological predictors of emergent psychopathology and substance use can be identified, this may provide invaluable information for the development of neurobiologically targeted prevention strategies. This review outlines longitudinal studies that identify neurobiological predictors of emergent psychopathology (depression, anxiety and substance use) and the escalation of symptom/use severity, as well as studies that have identified potential targets for successful treatment intervention (i.e. a reduction in symptoms/use severity). An emphasis is placed on convergent neurobiological targets for both emergent mental health issues and emergent substance use (Figure 1). It is important to note that only studies where neuroimaging data are used to predict future symptoms/use or change in symptoms/use between baseline and follow up are included, and studies that demonstrate associations between changes in brain structure/function and changes in symptoms/use (i.e. using multilevel modeling) are not discussed, as the temporal nature of these associations cannot be determined. Furthermore, while a majority of the studies outlined in this review

investigate the degree of symptomology in a sub-clinical population, when a clinical diagnosis is reported, it is explicitly noted.

Depression

Predictors of onset and future symptoms severity

Numerous cross-sectional and longitudinal studies have previously examined associations between depression and frontolimbic structures (for review, see Schmaal et al., 2017). Longitudinal research has also identified neurobiological risk factors for depressive symptom onset, specifically in adolescent populations. In particular, several structural MRI studies have shown volumetric alterations in frontal, limbic and white matter structure as predictors of adolescent depression onset. One recent study focusing on subcortical structures found that increased amygdala volume, between early-to-mid adolescence, was associated with major depressive disorder onset in late adolescence (females only), whereas decreased amygdala volume over time was associated with major depressive disorder onset in males (Whittle et al., 2014a). In this same study, they found that reduced hippocampal volumetric growth over time from early-to-mid adolescence was associated with onset of major depressive disorder in late adolescence. Further, smaller hippocampal volumes at baseline have been shown to predict increased depressive symptoms 18 months later in a sample of healthy adolescents (Pagliaccio et al., 2014), and in another sample, smaller baseline hippocampal volumes predicted depressive episode onset during follow up (average of 3.2 years), when controlling for early life adversity (Rao et al., 2010). Contrary to these findings, in a sample of predominantly healthy adolescents exposed to varying levels of maternal aggressive behavior, larger bilateral hippocampal volumes at baseline predicted increased depressive symptoms 2 years later in females only (Whittle et al., 2011). This sex-specific directionality, in harmony with previously mentioned amygdalar findings (Whittle et al., 2014), further supports research suggesting that male and female adolescents are likely at different points in non-linear limbic structure growth trajectories (Ostby, Tamnes et al. 2009). Although limited, previous research has also examined altered cortical gray matter development as a predictor of adolescent depression onset. One recent study, using machine learning in a sample of 10 to 15 year old females (with and without familial history of depression), found that adolescent girls who went on to develop major depressive disorder had thicker gray matter of the left insula and thinner gray matter of the right medial orbitofrontal cortex at baseline (Foland-Ross et al., 2015), prior to symptom onset.

In addition to autonomous atypical cortical and limbic structural volumes, prior research has also suggested an important structural relationship between prefrontal cortices and core limbic structures (Albaugh et al., 2013). While structural connectivity of these regions has not yet been explored as an independent predictor of depressive symptoms, one study in a sample of adolescents exposed to childhood maltreatment, without previous history of psychopathology, found that white matter disturbances (lower fractional anisotropy – FA – as measured by diffusion tensor imaging) of the left and right superior longitudinal fasciculus and right cingulum bundle at baseline predicted increased risk for unipolar depression onset, at an average follow up of 3.5 years, during adolescence (Huang et al., 2012). Collectively, these findings suggest that reduced limbic structure volumes, with the

exception of increased amygdalar volume in females, thicker gray matter of the left insula and thinner gray matter of the right medial orbitofrontal cortex (females only), and reduced FA of white matter tracts serving connectivity of limbic and frontal regions may serve as neurobiological risk markers for depressive symptom onset during adolescence.

In addition to structural neurobiological risk markers, several task-based functional MRI studies have implicated altered brain activation in frontal and limbic regions with onset of major depressive disorder or escalation of symptomology. First, various reward-based decision-making paradigms have been used to demonstrate that reduced ventral striatal activation in healthy adolescents is predictive of future escalations in depressive symptoms or future clinical diagnosis. Lower baseline ventral striatal activation during eudaimonic decisions (decisions involving self-sacrifice) when compared to hedonic (reward-based) decisions, (Telzer et al., 2014) and during reward anticipation (Morgan et al., 2013), were predictive of greater increases in depressive symptoms across 1 and 2 years of follow-up, respectively. Further, a greater reduction in ventral striatal activation during reward processing between baseline and two-year follow-up was associated with more depressive symptoms at follow-up (Hanson et al., 2015), and lower ventral striatal activation during reward anticipation at baseline predicted transition to subthreshold or clinically diagnosed major depressive disorder two years later in previously asymptomatic adolescents (Stringaris et al., 2015). Meanwhile, prefrontal activation during reward- and loss-based decision making is also predictive of future depressive symptom severity. In healthy adolescents, greater ventromedial prefrontal cortex activation during reward receipt at baseline (males only) (Hanson et al., 2015) predicted a greater increase in depressive symptoms across a 2 year follow-up, while reduced orbitofrontal cortex activation during loss at baseline (females only) predicted greater depressive symptoms at a 9 month follow-up (Jin et al., 2017), with greater orbitofrontal-posterior insula connectivity during loss also being associated with greater future depressive symptoms. In addition to studies looking at reward-based decision making, another study used task-based functional MRI during a peer exclusion task, and found that in healthy adolescents, greater subgenual anterior cingulate cortex activation during exclusion was associated with greater increases in parent-reported adolescent depressive symptoms during the following year (Masten et al., 2011). These findings suggest that reduced brain activation in limbic regions and altered activation in prefrontal regions of the brain, particularly during reward-based decision making, may serve as significant predictors for future increases in depressive symptoms to the extent of possible clinical diagnosis.

Studies using resting-state functional MRI, a method for measuring regional interactions of neural response when subjects are not engaged in a task, have also investigated the role of frontolimbic circuitry in predicting escalation of depressive symptoms. First, in unmedicated adolescents with major depressive disorder, reduced functional connectivity between the amygdala and insula at baseline was associated with greater increases in depressive symptoms 3 months later (Connolly et al., 2017). Furthermore, baseline asymptomatic adolescents who showed a significant increase in depression symptoms at follow up (between 6 and 54 months) had reduced baseline connectivity between the amygdala and the inferior frontal, supramarginal and mid-cingulate gyri at baseline, when compared to adolescents who showed no change in depressive symptoms (Scheuer et al., 2017). Lastly, in

healthy adolescents, a decrease in functional connectivity between the subgenual anterior cingulate cortex and the dorsal medial prefrontal cortex, posterior cingulate cortex, angular gyrus and middle temporal gyrus, between baseline and follow-up (average of 2 years) was associated with higher depressive symptoms at follow-up (Strikwerda-Brown et al., 2014). Taken together these studies suggest that reduced functional connectivity both within limbic regions, and between limbic and prefrontal regions pertinent for executive control, as well as a weakening of the connectivity of these regions across time, may serve as a risk marker for greater depressive symptoms later in life.

Predictors of treatment response

Though there have been several studies investigating potential neurobiological markers for successful treatment outcomes in adults with depression (for review, see Chakrabarty et al., 2016), the extension of these findings to adolescents has been limited. Two studies in adolescents with major depressive disorder found that lower subgenual anterior cingulate cortex activation to rewards vs losses (Straub et al., 2015), and lower resting state functional connectivity between the amygdala and both dorsolateral prefrontal and insular cortices (Straub et al., 2017), prior to treatment, predicted poorer treatment response (i.e. less reductions in depressive symptoms) following cognitive behavioral group therapy. This suggests that reward-related limbic activation, and functional connectivity within and between frontolimbic structures, may serve as an indicator for which individuals may benefit most from certain types of treatment. More importantly, these findings are in line with previous literature suggesting lower reward-related limbic activation, smaller limbic region volumes, and reduced connectivity within the limbic and frontolimbic systems are predictive of greater symptom severity and depression onset (see above).

Anxiety

Predictors of onset and future symptom severity

Converging with studies of depression, frontolimbic circuitry has also been implicated in emergent anxiety disorders during adolescence, based on numerous cross-sectional and associative longitudinal studies (for review, see Swartz and Monk, 2014); however, few studies have prospectively investigated neurobiological risk markers for the onset and escalation of anxiety symptoms. Those few prospective studies have found that in a sample of largely healthy adolescents, greater pituitary volume predicted higher anxiety symptoms three years later (Zipursky et al., 2011), and in a sample of adolescents both with and without childhood trauma, greater cortical thickness (indicative of delayed maturation) in the right middle temporal gyrus predicted higher anxiety symptoms two years later (Busso et al., 2017). However, both of these findings were limited by *a priori* region of interest (ROI) based hypotheses, so broader neurobiological association cannot be inferred. That is, Zipursky et al. (2011) limited their investigation to only the pituitary glands, while Busso et al. (2017) only investigated structural ROIs that had previously been shown in their analyses to be associated with childhood abuse exposure. Thus, neither study had the capacity to identify limbic structures (such as the amygdala or ventral striatum), which have previously been shown to be associated with adolescent anxiety disorders (Swartz and Monk, 2014).

Predictors of treatment response

Despite limited neuroimaging research predicting onset or symptom progression, several studies have used longitudinal designs to identify neurobiological targets (including frontolimbic brain regions) that prospectively predict a reduction in anxiety symptoms following treatment. Using an emotional face processing task, during functional MRI, it has been shown that lower brain activation in the amygdala when viewing fearful vs. happy faces, prior to treatment, has been shown to be predictive of poorer treatment response (smaller reduction in anxiety symptoms) in adolescents diagnosed with an anxiety disorder (predominately generalized) who received either CBT or treatment with fluoxetine (McClure, Adler et al. 2007). Using a similar task, prior to treatment, lower brain activation in inferior and superior frontal gyri when viewing threatening faces predicted poor treatment response (smaller reductions in anxiety symptoms) in adolescents diagnosed with an anxiety disorder (generalized, social or separation) who received either cognitive behavioral therapy or treatment with selective serotonin reuptake inhibitors (Kujawa et al., 2016). In addition to these frontal regions, they also found that lower brain activation in the precentral and postcentral gyri when viewing threatening faces, and lower brain activation in the postcentral gyrus when viewing happy faces, also predicted poorer treatment response. Furthermore, similar to the depression literature outlined in the previous section, Forbes et al. (2010) found that during reward anticipation, lower striatal activation (along with greater medial prefrontal cortex activation), prior to treatment, predicted a smaller reduction in anxiety symptoms in adolescents diagnosed with a major depressive disorder. Together, these studies demonstrate that task-related activation in limbic and prefrontal regions may serve as indicators for which individuals will benefit most from intervention. These findings parallel the depression literature described previously (i.e. lower limbic activation is associated with greater symptomology), and implicate both frontal and limbic regions as potential neurobiological targets for successful treatment interventions.

Substance Abuse

Predictors of onset and future use severity

Like depression and anxiety, substance use disorders have also been associated with structural and functional abnormalities in frontolimbic circuitry, implicated in cognitive control, motivated behavior, and emotional processing (Goldstein and Volkow, 2011; Kravitz et al., 2015; Wilcox et al., 2016). In contrast to the psychopathology described above, many more longitudinal studies have begun to disentangle the extent to which these abnormalities reflect premorbid risk factors for substance use, as opposed consequences of chronic alcohol and/or drug use (for a review, Squeglia et al., 2014a). Given high rates of co-morbidity with substance use, depression and anxiety may be attributable, in part, to common neurobiological risk factors for substance use. Below, we review the evidence that structure and function of frontolimbic circuitry predicts future initiation and escalation of substance use and treatment outcomes.

Studies of baseline gray-matter morphology have found that volume, thickness, and gyrification in frontolimbic regions predict the later initiation and escalation of substance use. In adolescents, thinner anterior cingulate and ventrolateral prefrontal cortices at a

baseline were associated with heavy alcohol use 3-years later (Squeglia et al., 2014b), and thinner dorsolateral prefrontal cortex predicted more binge drinking up to 13 years later (Brumback et al., 2016). Another study found that smaller anterior cingulate volume and higher levels of negative affect in 12 year olds increased the odds of experiencing alcohol-related problems 4 years later (Cheetham et al., 2014). Smaller volume in the nucleus accumbens at baseline has also been observed in adolescents who go on to initiate regular substance over the course of 2 years (Urosevic et al., 2015). Furthermore, smaller volume or less gyrification in the orbitofrontal cortex at baseline predicts initiation of cannabis use over the course of 4 years (Cheetham et al., 2012), the emergence of substance use disorders over the course of 6 years (Cheetham et al., 2017), and increases in alcohol-use related problems over the course of 2 years (Kuhn et al., 2016) during adolescence. However, other studies have not found significant associations between orbitofrontal morphometry at baseline and the initiation of alcohol use (Luciana et al., 2013; Squeglia et al., 2014b) or future episodes of binge drinking (Brumback et al., 2016). Taken together, these studies suggest that smaller volumes and thicknesses in frontolimbic regions predict future substance use. Lack of replicability across studies may be attributable to cross-study heterogeneity in participant characteristics and outcome measures, issues that may be ameliorated by studying larger samples.

Prospective studies designed to understand the etiology of substance use disorders have predominately measured brain function while participants are engaged in tasks that require executive functioning or reward processing. In substance-naïve adolescents, baseline activation in ventrolateral prefrontal cortex during reward-based risky decision making was lower in adolescents that went on to initiate binge drinking behavior (Jones et al., 2016). However, within a group of heavy cannabis users, greater activation in the dorsolateral prefrontal during risky decision making predicted increased cannabis use over the course of 6-months (Cousijn et al., 2013). These findings highlight how abnormalities in prefrontal circuitry during decision-making may perpetuate future substance use, but additional work is needed to fully disentangle substance-specific risk factors. Consistent with studies showing that striatal activation during reward processing predicted future symptoms of depression (Stringaris et al., 2015) and anxiety (Forbes et al., 2010), less activation in the nucleus accumbens, dorsolateral prefrontal cortex, and dopaminergic midbrain nuclei during reward anticipation at baseline (~14 years old) predicted problematic drug use by age 16 in novelty seeking adolescents (Büchel et al., 2017). This study also examined ventral striatal activation during reward anticipation in adolescents in the lower and middle quartiles on novelty seeking traits, but in these adolescents, there was no association between activation and problem drug use. This may explain why brain responses to reward were less important in predicting future alcohol use among adolescents than reward-related personality traits (e.g. novelty-seeking, impulsivity, sensation-seeking) and genetic variation in another study of the same participants (Heinrich et al., 2016).

Studies attempting to understand the etiology of substance use disorders have also examined brain function during response inhibition and working memory. In alcohol-naïve adolescents, less brain activation in the ventrolateral, dorsolateral, and medial prefrontal cortices, cingulate gyrus, and putamen during response inhibition was present in adolescents who initiated heavy drinking (4 years later) compared to those that continued abstaining or

that only engaged in minimal alcohol use (Norman et al., 2011). Similarly, another study found that less activation in the dorsolateral prefrontal cortex during failed inhibition, compared with correct inhibition, at baseline predicted the initiation of problem substance use approximately 4 years later (Heitzeg et al., 2014). In adolescents between the ages of 16 and 19 who had already initiated frequent alcohol use, less activation in the ventromedial prefrontal cortex during response inhibition predicted more symptoms of drug dependence and higher levels of drug use in the 18 months following the initial assessment (Mahmood et al., 2013b). While these studies suggest that less brain activation in the prefrontal cortex during response inhibition is a risk factor for the initiation and escalation of substance use, a study attempting to predict alcohol-induced blackouts detected a different pattern of results. In adolescents between the ages 12–14, those who experienced alcohol-induced blackouts in the 5 years following the baseline scan, had greater activation in dorsolateral prefrontal cortex during response inhibition compared with adolescents who go on to drink and do not experience blackouts and nondrinking controls (Wetherill et al., 2013). In the same study, adolescents who went on to drink but who did not experience blackouts had less activation than the control sample in the dorsolateral prefrontal cortex. Future studies should examine whether hyper- versus hypo-activation in the prefrontal cortex relative to the control sample reflects the degree of impairment in behavioral performance (Chung et al., 2013; Karlsgodt et al., 2009).

Another executive function that is believed to play a role in the development of addiction is working memory. Before the initiation of alcohol use, less activation in medial frontal cortex at baseline predicted the onset of heavy drinking over the course of 3 years (Squeglia et al., 2012). In contrast, a study of heavy cannabis users showed that network functioning within a frontoparietal network did not predict changes in cannabis or alcohol use over the course of three years (Cousijn et al., 2013). Although the association between mood disorders and cognitive functioning is understudied in adolescents, a recent review of the literature concluded that depression is associated with impairments in neuropsychological functioning across various cognitive domains including working memory (Baune et al., 2014). Prospective studies are needed to determine whether executive functioning and the underlying neural circuitry predict the emergence of depression and anxiety.

In addition to implicating frontolimbic brain regions in the onset and escalation of substance use, several others brain regions have also been identified. In particular, brain activation in parietal cortex (Jones et al., 2016; Mahmood et al., 2013b; Norman et al., 2011; Squeglia et al., 2012), temporal cortex (Cousijn et al., 2013; Jones et al., 2016; Norman et al., 2011; Wetherill et al., 2013) and cerebellum (Wetherill et al., 2013) during tests of executive functioning have been shown to predict future substance use. This finding suggests that, in addition to the convergence with findings in adolescent anxiety and depression highlighting the importance of frontolimbic circuitry, there are additional regions that may serve as unique predictors for the initiation of substance use.

Predictors of treatment response

Some preliminary studies indicate that neurobiological markers may also be useful for predicting treatment response for substance use disorders. One study used a reward cue

antisaccade task (requiring the inhibition of reflexive eye movements towards a cue) to assess brain function during cognitive control in adolescents who were engaged in or recently completed a community-based outpatient treatment for substance use disorders. In trials where successful inhibition was rewarded, less activation in the amygdala, nucleus accumbens, putamen, supplementary eye field, and ventrolateral prefrontal cortex at baseline predicted greater symptoms of marijuana dependence 6-months later (Chung et al., 2015). A study of adolescents who recently completed treatment for cannabis use disorder, found that lower functional connectivity between the caudal anterior cingulate and orbitofrontal cortex predicted greater amounts of cannabis use during the following 18-months (Camchong et al., 2017). In adolescents engaged in intensive outpatient substance use treatment, lower fractional anisotropy in prefrontal, orbitofrontal and temporal regions of interest were associated with greater alcohol problem severity 6 months after the scan. However, no associations were found between fractional anisotropy and marijuana-related outcomes (Chung et al., 2013). These studies suggest that structure and function of frontolimbic regions represent a risk factor for persistent substance use. More research is needed to determine how this information can be used to guide treatment decisions and the development of novel evidence-based interventions (for a review, Feldstein Ewing et al., 2016).

Conclusions

While many studies of adolescent neurodevelopment and emergent psychopathology still lack predictive validity, many conclusions can be drawn from recent literature investigating the temporal relationship between the two. The majority of the current studies investigating predictors of adolescent mental health issues implicate dysfunction in frontolimbic brain regions, a finding that overlaps significantly with research findings investigating emergent substance use. This body of work suggests that within limbic regions, smaller volumes and thinner cortices (Cheetham et al., 2014; Pagliaccio et al., 2014; Rao et al., 2010; Squeglia et al., 2014b; Urosevic et al., 2015; Whittle et al., 2014a) and reduced functional activation, particularly surrounding emotional (McClure et al., 2007) and rewarding stimuli (Buchel et al., 2017; Forbes et al., 2010; Hanson et al., 2015; Morgan et al., 2013; Straub et al., 2015; Stringaris et al., 2015; Telzer et al., 2014), appear to serve as a predictor for onset, escalation, and persistence of adolescent psychopathology. Additionally, smaller volumes and thinner prefrontal cortices (Brumback et al., 2016; Cheetham et al., 2012; Foland-Ross et al., 2015; Kuhn et al., 2016; Squeglia et al., 2014b) and reduced prefrontal activation during tasks involving rewarding and emotional stimuli (Buchel et al., 2017; Jin et al., 2017; Jones et al., 2016; Kujawa et al., 2016) and executive control (Heitzeg et al., 2014; Mahmood et al., 2013a; Norman et al., 2011) also appear to be associated with the onset, escalation, and persistence of adolescent psychopathology. Lastly, reduced functional connectivity both within limbic regions (Connolly et al., 2017), and between limbic and prefrontal regions (Camchong et al., 2017; Scheuer et al., 2017; Strikwerda-Brown et al., 2014), as well as smaller indices of white matter maturation (i.e. fractional anisotropy) in tracts serving limbic and frontal regions (Chung et al., 2013; Huang et al., 2012) may serve as a risk marker for greater psychopathological symptoms.

These findings are not surprising, given the developmental asynchrony of the frontolimbic system during the adolescent years (Mills et al., 2014; Simmonds et al., 2014), but they are by no means conclusive. Studies suggest that the predictive nature of these findings can differ based on sex (Foland-Ross et al., 2015; Hanson et al., 2015; Jin et al., 2017; Whittle et al., 2014a; Whittle et al., 2011), environmental variables (e.g. maternal aggression; Whittle et al., 2011), personality traits (e.g. novelty seeking; Buchel et al., 2017), and in the case of substance use, can vary based on the presence of substance-induced consequences (e.g. blackouts; Wetherill et al., 2013) or the drug under investigation (e.g. marijuana vs alcohol; Cousijn et al., 2013; Jones et al., 2016). In order to make better predictions about emergent psychopathology and resolve inconsistencies in the existing literature, we need large, prospective, longitudinal studies that simultaneously examine a wide range of potential causal factors and their interactions. For example, recent studies have used machine learning techniques in an attempt to predict future alcohol use from demographic information, neuropsychological functioning, personality, behavior, and assessments of brain structure and function. These studies found that neuroimaging biomarkers were among the variables important for predicting the initiation of future substance use (Bertocci et al., 2017; Squeglia et al., 2017; Whelan et al., 2014). Furthermore, environmental variables, such as parental stress, and personal mental health mental (i.e. higher depressive symptoms) have also been used to successfully classify individuals who will go on to engage in substance use (Bertocci et al., 2017).

The findings outlined in this review, although constrained, suggest that alterations in frontolimbic circuitry may serve as an important risk maker for future development of psychopathology, including mental illness and substance abuse, during adolescence. This knowledge is crucial, as it may provide a neurobiological target for future intervention and prevention strategies targeted at youth who are at-risk for developing these psychopathologies. Promising work has already suggested that environmental variables, such as positive parenting (Whittle et al., 2014b) may be associated with altered structural developmental trajectories of frontolimbic regions, and resting-state functional activation, may be altered following behavioral intervention strategies, such as cognitive behavioral therapy (Straub et al., 2017). With the guidance of predictive longitudinal neuroimaging findings, future studies may help elucidate the best treatment strategies for making targeted changes in the developing adolescent brain in order to treat and/or prevent the development of psychopathology during this sensitive period of development.

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Figure 1. Frontolimbic Circuitry Implicated in Emergent Psychopathology During Adolescence

The brain regions highlighted in cool colors represent regions implicated in executive functions, such as decision making, working memory and attention. The structures highlighted in warm colors are involved in reward and emotional processing. The coronal slice depicts the dorsolateral and ventrolateral prefrontal cortices (dlPFC, vlPFC), anterior cingulate cortex (ACC), insula (Ins), and nucleus accumbens (NAcc). The axial view depicts the ventromedial prefrontal cortex (vmPFC), subgenual ACC, amygdala and hippocampus. Brain regions were delineated using the Harvard-Oxford Probabilistic Atlas.