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Balancing act: Neural correlates of affect dysregulation in youth depression and substance use – A systematic review of functional neuroimaging studies

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ABSTRACT

Both depression and substance use problems have their highest incidence during youth (i.e., adolescence and emerging adulthood), and are characterized by emotion regulation deficits. Influential neurodevelopmental theories suggest that alterations in the function of limbic and frontal regions render youth susceptible to these deficits. However, whether depression and substance use in youth are associated with similar alterations in emotion regulation neural circuitry is unknown. In this systematic review we synthesized the results of functional magnetic resonance imaging (fMRI) studies investigating the neural correlates of emotion regulation in youth depression and substance use. Resting-state fMRI studies focusing on limbic connectivity were also reviewed. While findings were largely inconsistent within and between studies of depression and substance use, some patterns emerged. First, youth depression appears to be associated with exaggerated amygdala activity in response to negative stimuli; second, both depression and substance use appear to be associated with lower functional connectivity between the amygdala and prefrontal cortex during rest. Findings are discussed in relation to support for existing neurodevelopmental models, and avenues for future work are suggested, including studying neurodevelopmental trajectories from a network perspective.

1. Introduction

Arguably, the period from adolescence through emerging adulthood (i.e., from age 10 until the late twenties) is the most vulnerable period for the emergence of mental health disorders. The prevalence of psychiatric disorders during this period is estimated to be as high as 50 % (Blanco et al., 2008) and the incidence of specific disorders such as major depressive disorder (MDD) and substance use disorders (SUD) is the highest between adolescence and emerging adulthood compared to other life periods (Burke et al., 1990; Kessler et al., 2005; Rohde et al., 2013). Moreover, early depression and substance use disorders are associated with greater functional impairment, comorbidities, and contribute significantly to global disease burden in young people (Teesson et al., 2005; Toumbourou and Catalano, 2005; Zisook et al., 2007).

Furthermore, depression and substance use disorder often co-occur in individuals. For example, in a study of 6355 patients with alcohol and drug dependence, Miller et al. (1996) found that 44% of these individuals also had a lifetime history of depression. Similarly, SUDs appear to be as common in individuals with depression; in a study of depression, 33 % of patients with MDD also had symptoms consistent with a concurrent SUD (Davis et al., 2005, 2008). Although the frequency of the comorbidity between the two disorders has been well established, little is known about the mechanisms of this association. While a causal relationship could adequately explain the relationship (e.g., depression leading to substance use), it has been suggested that the two disorders may share a common etiological origin (Swendsen and Merikangas, 2000). Examples of shared aetiologic factors could include common genetic predisposition, or environmental risk factors such as childhood trauma (Swendsen and Merikangas, 2000). Importantly, it has been suggested that alterations in neural circuits underlying emotion regulation (which could be related to the genetic and environment factors outlined above) may represent a common risk mechanism for both depressive and substance use disorders (Bonelli and Cummings, 2007; Kober, 2014; Koob and Volkow, 2009; Price and Drevets, 2009).

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"Emotion regulation" is the process by which individuals exert control and thus regulate their experience and expression of emotions (Thompson, 1994). In healthy individuals, emotion regulation is suggested to be supported by prefrontal cortical (PFC) regions, including dorsolateral PFC, ventrolateral PFC, and anterior cingulate cortex, which modulate emotional responses in subcortical regions including the amygdala (Ochsner and Gross, 2008). Functional magnetic resonance imaging (fMRI) studies of depressed individuals, when compared to healthy controls, have shown evidence of hypo-activation of the PFC and hyper-activation of the amygdala, during emotion regulation tasks. This interaction between activation of the PFC and amygdala has been suggested to underlie efficient versus dysfunctional downregulation of negative emotions (Drevets, 1999). Alterations in the neural correlates of emotion regulation have similarly been implicated in substance use and SUD. For example, during an emotion regulation paradigm, compared to non-users, young adults who engage in substance use were found to have higher self-reported negative affect (i.e., lower emotion regulation success), as well as lower cortico-subcortical connectivity (Zimmermann et al., 2017).

The neural circuitry underlying emotion regulation undergoes marked development during adolescence and emerging adulthood. One of the most influential early set of findings from research on neurodevelopment reported that the brain, particularly the PFC, continues to undergo dynamic structural and functional development until the mid to late 20s (Cao et al., 2014; Casey et al., 2005, 2008; Fair et al., 2009; Gogtay et al., 2004; Sowell et al., 2004). These findings, in concert with evidence that subcortical regions develop relatively earlier than the PFC, prompted some influential theories suggesting that these changes may render individuals more vulnerable to the development of mental health problems marked by emotion dysregulation, including depression and SUD (Casey and Jones, 2010; Nelson et al., 2005; Steinberg, 2008).

"Dual systems" or "maturational mismatch" theories (Casey et al., 2008; Steinberg, 2008) propose that the social, behavioral and emotional changes observed in adolescence can be partially explained by the temporal mismatch between the protracted development of regulatory prefrontal regions, and the relatively quicker development of subcortical regions associated with reward and emotion processing (Casey et al., 2008). In addition, this developmental mismatch has also been discussed in the context of emerging adults, as developmental gains in impulse control occur throughout adolescence and well into the twenties (Steinberg, 2010b). An exaggeration of this temporal mismatch is suggested to be associated with poor regulation of bottom-up subcortical structures by top-down prefrontal regulatory structures, and may contribute to dysregulated affect, rendering individuals more susceptible to the development of depression (Nelson et al., 2005) or problems with substance use (Casey et al., 2008).

Although these theories have been influential, there have concerns raised about their broad application to explain a wide variety of phenomena (Pfeifer and Allen, 2012), suggesting that the model may lack specificity. In addition, the applicability of the dual systems model to MDD has been questioned because unlike SUDs, the incidence rates of MDD remains consistent from adolescence through to later adulthood (Davey et al., 2008). Accordingly, there have been calls to directly test more precise hypotheses derived from these theories (Pfeifer and Allen, 2016). In this respect it is notable that research directly testing whether the dual systems model is equally applicable to both MDD and SUD (and therefore may explain common etiological factors that contribute to comorbidity) is still somewhat lacking. Although such research would ideally require investigation of the coupling or coordinated function of neural systems over time, other research that might speak to the validity of these theories includes task-based studies investigating neural activation or connectivity associated with emotion processing and regulation in youth MDD or SUD populations. Further, research investigating subcortical resting state connectivity in MDD or SUD may provide insight into task-independent connectivity of networks implicated in dual-systems/mismatch models; however, there is currently no synthesis of such data to inform whether there is current support for the dual-systems/mismatch models in MDD or SUD, and importantly, whether there are nuances that discriminate MDD from SUD. The aim of this review is to examine the extant literature to evaluate the applicability of the dual systems/mismatch models to both depression and substance use.

2. Aims

This systematic review will focus on task-based and resting state fMRI studies in adolescents and emerging adults (i.e., youth) and compare the underlying neural circuitry between youth depression and substance use, with a focus on bottom up subcortical and top down regulatory structures highlighted by dual systems/mismatch models. Given that a) the developmental mismatch has been discussed in the context of adolescence extending into emerging adulthood (Steinberg, 2010b) the development of the prefrontal cortex is protracted, and continues well into the twenties (Cao et al., 2014; Casey et al., 2005, 2008; Fair et al., 2009; Gogtay et al., 2004; Sowell et al., 2004), and c) the incidence rates of MDD and SUDs are similar during adolescence and emerging adulthood (Burke et al., 1990; Kessler et al., 2005; Rohde et al., 2013), in our review, which sought to examine the usefulness of the dual systems model, we included both adolescent and emerging adult literature. Of note, evidence suggests that substance use in youth is often indicative of the development of substance use disorders in adulthood (DeWit et al., 2000; Grant et al., 2001; Jordan and Andersen, 2017). Given this, in addition to the small number of studies on SUD in youth, we included studies on substance use and abuse in addition to SUD.

Findings consistent with the model would include subcortical hyperactivity and aberrant prefrontal activity during tasks of conscious or unconscious emotion regulation. Findings consistent with the model would include subcortical hyperactivity and aberrant prefrontal activity during tasks that elicit conscious or unconscious emotion regulation processes. There are, however, some differences in the manner that these models have been applied to MDD and substance use. For example, striatal hypoactivation while processing positive stimuli has been suggested to characterize MDD, whereas striatal hyperactivation in response to positive stimuli may characterize substance use (Casey and Jones, 2010; Rive et al., 2013; Wilcox et al., 2016). As such, we predicted that we would see these differences emerge in our review of the empirical literature. Regarding prefrontal (top-down) regulatory structures, both exaggerated and attenuated activation could potentially be in agreement with the model. For instance, hypoactivation could suggest an inability to recruit cortical regions for top-down control (Colich et al., 2016), while hyperactivation could indicate compensatory recruitment (Rive et al., 2013). Thus, the review also set out to find a pattern in the reviewed studies with respect to hypoactivation and hyperactivation of regulatory structures. Regarding resting state functional connectivity (rsFC), we suggest that lower cortico-subcortical connectivity would be most consistent with the model, given that decreased rsFC has been suggested to reflect lower functional integration of cortical and subcortical structures, thus leading to a breakdown in the neural circuitry underlying emotion regulation (Connolly et al., 2017; Wang et al., 2012). This breakdown in the circuitry could potentially explain depression and substance-use associated emotion regulation deficits.

3. Materials and methods

3.1. Literature search

This systematic review was conducted using the PRISMA guidelines (Moher et al., 2009), and the protocol of the review was registered with PROSPERO (ID: CRD42019134674) after the literature search was conducted, but prior to data extraction and writing of the manuscript (submitted 13/5/2019, updated/revised 11/07/2019, and accepted

11/11/2019; registered protocol available in Supplementary Material). Literature searches were conducted for English language papers using three databases; Medline, PsycInfo and Embase. Search results were extracted on 30th November 2018 with no restrictions on dates. Two different searches were conducted and then combined; 1) fMRI studies using emotion regulation or processing tasks and 2) studies using resting-state fMRI focusing on subcortical connectivity in youth depression and substance use (search algorithms can be found in supplementary material). The search was re-run closer to the finalization of the manuscript (1st July 2019) to ensure recent published literature was included.

3.2. Study selection

Duplicated papers were removed, and titles and abstracts were then assessed through Covidence (Veritas Health Innovation, Melbourne, Australia) for inclusion. One author screened the articles and abstracts of the deduplicated set of search results in order to exclude the ineligible articles. Two authors assessed the eligibility of the remaining articles reaching 100% agreement.

3.3. Inclusion and exclusion criteria

Studies were included if they i) utilized fMRI (task-based and/or resting state) and for task-based fMRI, the tasks involved were those intended to evoke an emotion response; ii) included individuals with a current, past, or persistent diagnosis of depressive disorder, or individuals with substance use/abuse/dependence (correlational studies of depressive symptoms or substance use were also included); iii) included human participants and samples with a mean age in the range of 10–29 years (WHO, 2015; Arnett et al., 2014); and v) were published in English.

We included task-based fMRI studies that examined activation and/or connectivity. In addition, we included resting-state fMRI studies that focused on connectivity between emotion generating and processing regions (amygdala, basal ganglia, insula) and their connectivity with frontal and other cortical regions. With respect to resting state, we included only papers that used seed-based connectivity analyses or ICA studies studying subcortical network connectivity, given that results using other approaches, such as regional homogeneity, amplitude of low-frequency fluctuations, graph theory and network brain statistics are not comparable to seed-based connectivity analyses, the most common method used.

3.4. Data extraction and synthesis

For each study, we extracted the following information i) participant mean age and age range, ii) number of participants iii) participant sex, iv) medication status of participants, v) existing comorbidities in participants, vi) task used if applicable, vii) analysis method used and contrasts examined for task-based studies, viii) statistical correction methods used, and ix) significant findings. Significant findings of interest included i) group differences in regional brain activation for task fMRI, ii) group differences in task-dependent functional connectivity (psychophysiological interaction analyses (PPI)), iii) group differences in resting state functional connectivity, and iv) associations between neural activity and measures of depression and substance use based on correlation or regression. The number of studies that reported a specific finding were recorded for the aggregate data synthesis. A formal meta-analysis was not performed due to the heterogenous nature of the reviewed studies with respect to clinical diversity of the patient population, task paradigms and analysis approaches.

For task-based studies, the data synthesis was divided based on the contrast reported by studies; positive (positive > negative/neutral/fixation contrasts), negative (negative > positive/neutral/fixation contrasts) and emotion (all emotions > shapes/fixation/rest). Emotions were aggregated into positive and negative due to the small number of studies for each specific emotion (e.g., sadness, fear, happiness and anger). A few studies (Diler et al., 2013; Mattson et al., 2016; Pan et al., 2013; Whalley et al., 2015) reported neutral vs baseline results, which were included with the all emotions category and did not introduce any inconsistencies. Studies using cognitive modulation paradigms were also grouped based on contrasts (e.g., attend > reduce, reduce > attend). Longitudinal imaging studies, if any, are identified separately in each section.

4. Results

4.1. Literature search

Our search yielded 826 unique peer reviewed papers in English, of which 705 assessed topics not relevant to this review. Full text review led to the exclusion of 33 studies due to participant age and the task paradigm used. After full text review, four additional studies were excluded, and 84 studies were retained for the systematic review. Eleven additional articles were identified through manual searches. Thirty-four articles emerged from the search re-run on 1st July 2019, of which three were deemed suitable for inclusion. The total number of studies included was thus 98 (Supplementary Fig. 1).

4.2. Dimensions of emotion regulation

Task-based fMRI studies were classified according to a conceptual approach used previously. Based on previous approaches and interpretations, Wilcox et al. (2016) posited four different dimensions of emotion regulation: affect intensity/reactivity, affective modulation, behavioral control, and cognitive modulation. Briefly, affect intensity/reactivity is the rapid response to affective stimuli before top-down regulatory mechanisms are engaged. Affect reactivity tasks involve the rapid presentation (<2 s) of emotional cues. Affective modulation on the other hand refers to the engagement of processes involved in the assessment of emotional salience, threat and other environmental cues. In affective modulation paradigms, participants are exposed to longer emotional cues, which allows for the engagement of top-down regulatory processes. Behavioral control is the control of impulsivity in the face of emotion, and is commonly assessed by tasks that assess the effect of emotional distractors. Cognitive modulation involves a direct and deliberate engagement of said regulatory processes, and related paradigms require participants to reappraise or reinterpret a stimulus in order to alter their emotional response (Wilcox et al., 2016).

Due to the small number of identified studies that utilized affect intensity/reactivity tasks (n = 4 in depression and n = 0 in substance use), this dimension was combined with affect modulation studies, given that both dimensions tap into automatic emotion generation and processing. In spite of small numbers, studies employing behavioral control and cognitive modulation paradigms were not combined as they tap into distinct emotion regulation processes (Wilcox et al., 2016). See Table 1 for number of studies in each emotion regulation dimension and resting state.

Table 1
Number of studies identified using the search for each dimension of emotion regulation and resting state in depressed and substance using youth.

	Depression	Substance Use
Affect reactivity/modulation	31	7
Cognitive modulation	6	1
Behavioral Control	9	2
Resting State	29	13
Total	**75**	**23**

4.3. Regions implicated in emotion regulation

In order to consolidate the results from the studies, we clustered regions into six different groups, based on Wilcox et al. (2016) (Fig. 1). The regions of focus fall under two broad categories, emotion generating (EG) and emotion regulating (ER); i.e. 1) amygdala (EG1), 2) insula (EG2) and 3) basal ganglia (EG3) in the former category, and 4) dorsomedial PFC (dmPFC, ER1) (including the dorsal anterior cingulate cortex (dACC) and the supplementary motor area (SMA) and Pre-SMA ;), 5) lateral PFC (lPFC, ER2) (including the dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC) and lateral orbitofrontal cortex (lOFC)), and 6) the rostral ACC/ventromedial PFC (rACC/vmPFC, ER3) (including the pregenual ACC (pgACC), subgenual ACC (sgACC), and medial OFC (mOFC), in addition to the hippocampus (HPC) and parahippocampus (paraHPC)). This grouping is based on the functions of these regions and the role they each play in emotion generation, processing and regulation. The amygdala, insula and the basal ganglia have a well-established role in emotion processing and are frequently activated during tasks involving affective reactivity (Duval et al., 2015; Etkin and Wager, 2007). Although the basal ganglia was not included in Wilcox et al.'s review, it is included here given that the striatum and nucleus accumbens are known to have key roles in processing of positive emotion and reward (Callaghan et al., 2017; Rzepa and McCabe, 2016).

It is hypothesized that affect is downregulated by frontal regulatory regions, automatically by the rACC/vmPFC, and consciously or voluntarily by the lPFC in emotion-cognition interactive processing, and by the dmPFC in explicit emotional evaluation and regulation (Lee and Siegle, 2012; Wilcox et al., 2016). The three structures (i.e., dmPFC, lPFC and rACC/vmPFC), play distinct functional roles in emotion processing and regulation. The dmPFC is part of the salience network and is activated in response to salient positive and negative cues. It is also involved in the emotional response during goal selection (Duval et al., 2015; Phillips et al., 2008; Uddin, 2015). The lPFC has been suggested to be involved in the planning and selection of goals, working memory, and voluntary regulation of emotion generating regions (i.e. amygdala and insula) (Duval et al., 2015; Phillips et al., 2008; Uddin, 2015), The rACC/vmPFC is posited to be involved in assigning motivational value to salient cues, emotional decision making, processing emotional conflict, and automatic or involuntary regulation of emotion generating regions (i.e. amygdala, insula) (Phillips et al., 2008; Viviani, 2014). We also chose to include the hippocampus and parahippocampus with the rACC/vmPFC group because of its role in automatic emotion regulation (Phillips et al., 2008). For the sake of readability, in text we refer to the three groups of structures, i.e. ER1, ER2 and ER3, as dmPFC, lPFC and rACC/vmPFC respectively.

4.4. Synthesis of results

4.4.1. Depression

4.4.1.1. Affective reactivity and affective modulation. Our search yielded the largest number of studies for this dimension in youth depression; 31 (Table 2). Most studies used emotion face processing tasks except three (Strigo et al., 2013, 2008; Whittle et al., 2012).

Depression-associated hyperactivation of emotion generating regions was consistently reported across studies (Fig. 2A). Amygdala hyperactivation was observed in response to negative stimuli in several studies (n = 8/23; the number of studies that used negative stimuli and conducted whole-brain analyses and/or used the amygdala as a region of interest, ROI); however, some studies also reported hypoactivation of the amygdala to negative stimuli (n = 2/23). While several studies noted depression-associated alterations in the reactivity of prefrontal structures to negative stimuli, the direction of this alteration was inconsistent. For instance, Hall et al. (2014) and Pan et al. (2013) found decreased activation of sgACC and vmPFC respectively, both of which are automatic emotion regulating structures (ER3), while for the same or neighboring regions (vmPFC and mOFC), Henderson et al. (2014) and Tao et al. (2012) found increased activation.

Regarding positive emotional stimuli, most of the included studies did find depression-associated brain activation; however, in those that did, the implicated regions, and the direction of the activity (higher vs lower), were not consistent (Fig. 2A). For instance, Quevedo et al. (2018) found higher amygdala activation for happy faces in depressed adolescents whereas Redlich et al. (2018) found lower amygdala activation for happy faces. For the all-emotions contrast (which includes neutral faces), studies reported depression-associated hyperactivation of the amygdala (n = 4).

Ten studies using affective reactivity/modulation paradigms conducted PPI analyses and demonstrated task dependent altered connectivity between the amygdala, insula, and emotion regulatory regions in depressed youth (Table 3). Two studies found higher depression-related connectivity between the insula and frontal regions for negative stimuli (Henje Blom et al., 2015; Strigo et al., 2013); however, there were few other consistent findings, and some opposing findings. For example, using a similar paradigm, studies found both increased (Matthews et al., 2008) and decreased (Musgrove et al., 2015) amygdalar-connectivity to ER3 (rACC/vmPFC) regions for all faces > baseline.

In summary, there were some consistent findings for affective

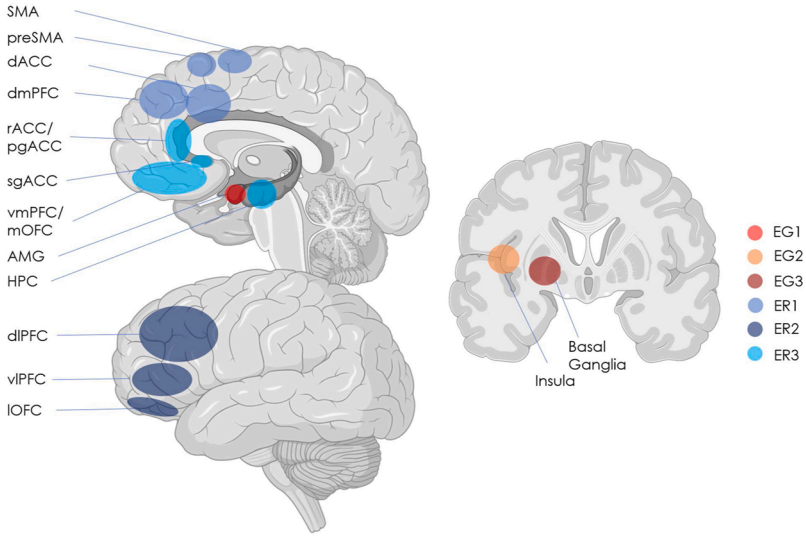

Fig. 1. Regions involved in emotion generation, processing and regulation. Regions colored orange and red (EG1: amygdala, EG2: insula and EG3: basal ganglia) are regions involved in emotion generation and processing; regions depicted in blue and purple are top-down regulatory structures (ER1: dmPFC, dACC, SMA, preSMA, ER2: dlPFC, lOFC, vlPFC, ER3: rACC, vmPFC, sgACC, HPC). Abbreviations: EG = emotion generating, ER = emotion regulating. Brain regions: ACC = anterior cingulate cortex, AMG = amygdala, dACC = dorsal ACC, dmPFC = dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, HPC = hippocampus, lOFC = lateral orbitofrontal cortex, mOFC = medial orbitofrontal cortex, pgACC = perigenual ACC, preSMA = presupplementary motor area, rACC = rostral ACC, SMA = supplementary motor area, sgACC = subgenual ACC, vlPFC = ventrolateral prefrontal cortex, vmPFC = ventromedial prefrontal cortex. (For interpretation of the references to colour in the Figure, the reader is referred to the web version of this article).
Brain Images were downloaded from BioRender.

Table 2
Depression-associated aberrant activation during affective reactivity/modulation paradigms.

Study	Methodological aspects						Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Task	Statistical Threshold and analysis method	ROI for activation analysis	Contrast	Regions	Recruitment/ connectivity in DEP vs HC
Altinay et al. (2016)	Anxious MDD: 15 (9 F)	27	18-60	Matching faces on emotion or gender	ROI ROI: CT $p < 0.05$, $k >= 44$ CDT $p < 0.05$ WB: CT $p < 0.05$ $k >= 219$ CDT $p < 0.01$	AMG	Negative	AMG	Higher
Beesdo et al. (2009)	Total MDD = 26 (15 F) Only MDD (without anxiety) = 12 (7 F)	Total MDD = 14.08, Only MDD = 14.2	NR	Matching faces on emotion or gender	WB and ROI Greenhouse Geiser correction	AMG, OFC	Fearful-rated > fearful-passive	AMG	Higher
							Fearful > happy passive	AMG	Lower
Chan et al. (2016)	MDD = 30 (22 F)	23.4	NR	Matching faces on emotion or gender	WB and ROI CT FWE $p < 0.05$ CDT $p < 0.001$	AMG, HPC, ACC	Angry > baseline	sgACC	Higher
Dedovic et al. (2016)	Previously depressed = 14 F	20.13	18-25	Social evaluation task	WB and ROI CT FDR $p < 0.05$ k by MC CDT $p < 0.001$	dACC	Previously depressed females (PD) showed an increase in dACC activity over repeated bouts of social evaluation (from first evaluation to second evaluation) whereas HC exhibited a decrease. PD subjects had significantly higher dACC activity than HC at t2. They also found that (among the PD subjects) the greater the increase in dACC activity from first to second evaluation, the lower the depressive symptoms on the day of the evaluation and at the 6-month follow up.		
Diler et al. (2013)	MDD = 10	15.19	12-17	Matching faces on emotion or gender	WB CT $p < 0.05$ k by MC	WB	Happy	L Front precentral cortex	Lower
								R STG	Lower
								R PHG	Lower
							Neutral	L LOC	Higher
							Fear	L postcentral cortex	Higher
								R STG	Higher
								R OC	Higher
Fowler et al. (2017)	Total sample = 41	15.42	NR	Matching faces on emotion or gender	ROI and PPI CT $p < 0.05$ CDT $p < 0.001$	AMG	Negative rated > negative passive	AMG-vlPFC (PPI)	Higher
Gard et al. (2018)	Total sample = 167 (0 F) (Pitt Mother & Child Project)	~20 (exact mean not reported), fMR	~20-22 (Exact range not reported)	Matching faces on emotion or gender	WB and ROI CT FWE $p < 0.05$	AMG	Fear	L AMG - L MFG (PPI)	Lower
							Neutral	R AMG - L IFG (PPI)	Higher
Hall et al. (2014)	MDD = 32 (25 F)	15.54	12-19	Cued emotional pictures	WB and ROI CT (GRF) $p < 0.05$ CDT $Z > 1.94$	AMG, rACC, sgACC, Insula	Fear > happy	B AMG	Higher
								R STG/MTG	Higher
								Heschl's gyrus	Higher
								Insula	Higher
							Fear > happy	sgACC*	Lower
Henderson et al. (2014)	MDD = 19 (16 F)	17.3	12-20	Emotional of physical judgement of faces	WB CT $p < 0.05$ $k > 607$ CDT $p < 0.005$	WB	Sad	R Thalamus**	Higher
								L Putamen	Higher
								L AMG	Higher
								L Ant Insula	Higher
								R vmPFC	Higher
								R Fusiform gyrus	Higher
								L postCG	Higher
								R dACC	Higher
							Fear	B Thalamus	Higher
								R Ant Insula	Higher
							Neutral	R preCG*	Lower
								L vlPFC	Lower
Henje Blom et al. (2015)	MDD = 38 (28 F), scan data used for 31 (22 F)	16 (for 38)	13-18 (for 38)	Emotional of physical judgement of faces	WB and ROI for PPI CT $p < 0.05$ k by MC CDT $p < 0.05$	WB	Sad > happy	B Fusiform G	Higher
							Sad > happy	R Lingual G	Lower
							Happy > sad	B Fusiform G	Lower
								R Cerebellum	Lower
							Happy > sad	R Thalamus	Higher
							Happy > sad	L AMIC	Lower

(*continued on next page*)

Table 2 (*continued*)

Study	Methodological aspects						Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Task	Statistical Threshold and analysis method	ROI for activation analysis	Contrast	Regions	Recruitment/ connectivity in DEP vs HC
Ho et al. (2014)	MDD = 19 (11 F)	15.8	13-17	Matching faces on emotion or gender	WB and ROI for PPI CT $p < 0.05$ k by MC CDT $p < 0.05$	WB	Happy > sad	AMIC - Fusiform G, AMG, MFG (PPI)	Higher
							Fear strong > fear neutral	L Precuneus	Lower
								L ACC	Lower
								R preCG	Lower
							Fear strong > fear neutral	R sgACC- L Fusiform Gyrus, R Precuneus, R MFG (PPI)	Higher
							Fear strong > fear neutral	L sgACC - L Insula, Cingulate (PPI)	Higher
								mPFC	Lower deactivation
								PCC	Lower deactivation
Ho et al. (2015)	MDD = 26 (19 F)	16.1	13-17	Matching faces on emotion or gender	WB and PPI CT $p < 0.05$ k by MC	WB	Emotion processing	mPFC - B Precuneus, Cingulate G ***, L IPL/ SMG (PPI)	Higher
								PCC - B Precuneus, R Cingulate G, L Lentiform nucleus/ subcallosal cingulate gyrus (PPI)	Higher
Jenkins et al. (2016)	rMDD = 32 (21 F)	21.53	18-23	Matching faces on emotion or gender	WB and ROI CT $p < 0.05$ k > 55 CDT $p < 0.005$	AMG, sgACC	Faces > animals	L SFG	Higher
								Fusiform Cortex	Higher
								STG	Higher
								MTG	Higher
								SMG	Higher
								LOC	Higher
								AMG	Higher
Kerestes et al. (2016)dd	MDD = 29 (18 F), MDD risk = 39 (21 F)	MDD = 16.0, Mood risk = 13.4	8-17 (for total sample)	Matching faces on emotion or gender	WB and ROI for PPI CT $p < 0.05$ k by MC CDT $p < 0.005$	WB	Happy	dlPFC - vlPFC (PPI)	Lower
Matthews et al. (2008)	MDD = 15 (12 F)	24.5	19-30	Matching faces on emotion or gender	ROI CT $p < 0.05$ k by MC CDT $p < 0.05$	AMG	All faces > shapes	AMG	Higher
							All faces > shapes	AMG – sgACC and supragACC (PPI)	Higher
Mattson et al. (2016)	Total sample = 167 (0 F) (Pitt Mother & Child Project)	~20 (exact mean not reported), fMRI	~20-22 (Exact range not reported)	Matching faces on emotion or gender	ROI CT FWE $p < 0.05$	AMG	Neutral > shapes	AMG	Higher
Musgrove et al. (2015)	MDD = 27 (20 F)	15.7	12-19	Matching faces on emotion or gender	ROI, DCM CT $p < 0.05$	AMG, sgACC, supragACC, Fusiform gyrus, Inferior occipital gyrus	Negative emotion > fixation	L AMG	Higher
								L HPC	Higher
								L paraHPC	Higher
								Temporal pole	Higher
							Negative emotion > fixation	R AMG- R sgACC (PPI)	Lower
Pan et al. (2013)	MDD = 29 (19 F)	ATT = 16.2, NAT = 15.9	NR	Matching faces on emotion or gender	WB and ROI for PPI CT $p < 0.05$ k by MC CDT $p < 0.05$ group comparison $p < 0.008$	WB	Angry	B Primary SC	Higher
								R ACG	Higher
								R vmPFC	Higher
							Happy	L Primary SC	Lower
								R ACG	Lower
								L MFG	Lower
Quevedo et al. (2018)	MDD, dysthymia and depressive disorder = 43 (22 F)	14.73	NR	Matching faces on self or other	WB CT $p < 0.001$ k by MC CDT $p < 0.001$	WB	Bilateral medial temporal clusters: Depressed youth show less medial temporal limbic activity to the happy expression versus the neutral expression		

(*continued on next page*)

Table 2 (*continued*)

Study	Methodological aspects						Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Task	Statistical Threshold and analysis method	ROI for activation analysis	Contrast	Regions	Recruitment/ connectivity in DEP vs HC
							during self-recognition. Depressed youth exhibited more activity for the happy vs. the neutral expression during recognition of the other face while controls did not differ in activity for the same comparison. Main effect of group: Depressed group had lower activity in the cuneus but higher activity in postcentral and precentral gyri compared to the control group for all conditions. Medicated youth showed lower activity in the right superior and inferior parietal lobule,, and in the left and right IFG and MFG in all conditions.		
Redlich et al. (2018)			MDD = 20 (12 F)	16	15-18	Matching faces on emotion or gender	WB and ROI CT FWE p < 0.05	AMG	Negative faces AMG
Higher Positive faces	AMG	Lower							
Sabatinelli et al. (2015)	Dysphoric (moderate to severe depression based on BDI-II score) = 9 (0 F)	19.8	NR	Cues emotional images	ROI, GCA CT FDR p < 0.05 k > = 3	AMG, Ventral striatum and mPFC	Dysphoric participants showed on reliable modulation of mPFC activity by the category of images presented where the HCs did not. VS activity also did not show a reliable effect of picture content in the dysphoric group. On analysis of GC between the 3 seeds of interest, dysphoric group had weaker GC coefficients across all 6 Regions/Influence Targets. In addition, relative to the controls, dysphoric participants showed evidence of weaker modulatory influence of mPFC and VS on each other and on amygdala.		
Strigo et al. (2013)	MDD = 31 (15 F)	27.6	NR	Pain anticipation paradigm	WB and ROI for PPI CT p < 0.05 k > = 768 mm3 CDT p < 0.05	WB	High vs low pain anticipation	R ventral AI L MFG L Cingulate L STG	Higher Higher Higher Higher
							High vs low pain anticipation	R dlPFC R OFC	Lower Lower
							High vs low pain anticipation	R Post. Thalamus - R mPFC (PPI) R IFG – Cerebellum (PPI)	Higher Higher
Strigo et al. (2008)	MDD = 15 (12 F)	24.5	NR	Pain anticipation paradigm and CPT	WB and ROI WB: CT p < 0.05 k by MC CDT p < 0.05 ROI: SVC k > = 128 ul	AMG	High vs low pain anticipation	B Insula L IFG B dACC R dlPFC L dlPFC Caudate B Precuneus R PCC Brain stem AMG	Higher Higher Higher Higher Higher Lower Lower Lower Lower Lower
							High vs low pain	L PHG L OC R dlPFC R rACC	Higher Higher Lower Lower
							High vs low pain	Temporal lobe Precuneus Cerebellum PAG	Lower Lower Lower Lower
							High vs low pain	AMG	Higher
Tao et al. (2012)	MDD = 19 (11 F)	14.2	11-17	Matching faces on emotion or gender	WB and ROI WB: CDT p < 0.001 (unc) ROI driven by activation for fearful > neutral, SVC at p < 0.05	AMG, sgACC and OFC	Fearful > neutral	Frontal lobe B Temporal lobe B Putamen B Insula Cingulate Gyrus AMG HPC	Higher Higher Higher Higher Higher Higher Higher

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Table 2 (*continued*)

Study	Methodological aspects						Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Task	Statistical Threshold and analysis method	ROI for activation analysis	Contrast	Regions	Recruitment/ connectivity in DEP vs HC
								R OC	Higher
							Fearful > neutral	sgACC	Lower
Thomas et al. (2001)	MDD = 5 (5 F)	12.3	8-16	Cues emotional faces	ROI CT p < 0.05 k > = 3	AMG	Fearful > fixation	AMG	Lower
Van den Bulk et al. (2014)	Anxiety + Depression = 25 (21 F), MDD = 7, Dysthymia = 10	15.44 for all 25	12-19	Emotion face processing task with constrained and unconstrained attention	WB and ROI CT FDR p < 0.05 k > = 10	AMG		None	
Van Hoof et al. (2017)	Depressive disorders and/or anxiety (DEP) = 26 (22 F)	15.98	12-20	Emotion face processing task with constrained attention and unconstrained attention	WB and ROI CT FDR p < 0.05 k > = 10	DLPFC, amygdala, insula, thalamus, mid-cingulum, hippocampus.	**Whole brain analysis:** No significant differences in activation between the groups. **ROI analysis: HPC: State*emotion*group*hemisphere interaction:** post-hoc analysis showed more R HPC activation compared to L HPC activation in the DEP group (happy faces within 'how afraid are you?' and neutral faces within 'how wide is the nose?'). There was more left HPC activation for fearful > neutral within the state question 'how happy are you?' in HCs. In the DEP group, there was more left HPC activation for happy > neutral within the state question 'how wide is the nose?'. **Mid-cingulate: State*emotion*group interaction:** Post- hoc comparisons showed more deactivation in left mid cingulate compared to right mid cingulate for the HCs ('how afraid are you?'; 'how wide is the nose?', and the adolescents with internalizing disorders ('how wide is the nose?').		
Whalley et al. (2015)	High risk (HR) group = 81 at T1, HR MDD group at T2 = 20/81 (12 F), HR MDD group at T3 = 11/61	At T2 HR MDD = 22.51	16-25	Emotional judgement of images	WB CT FWE p < 0.05 CDT p < 0.001	WB	Positive > baseline	Thalamus*	Higher
							Neutral > baseline	Thalamus	Higher
							Positive > baseline	Insula	Higher
							own-mother positive > rest	ACC	Higher
Whittle et al. (2012)	Depressive symptomatology = 30 (18 F)	17.35	NR	Watching own/ familiar mother's affective behavior	WB CT p < 0.05 CDT Z > 3.1	WB		rACC	Lower
							Positive > neutral	right LOC	Lower
								R Putamen	Lower
Yang et al. (2010)	MDD = 12 (5 F)	15.9	14-17	Matching faces on emotion or gender	WB and ROI WB: CT p < 0.05 k by MC ROI: CT p < 0.05 CDT p < 0.0027 k by MC	AMG	All faces vs shapes	L AMG*	Higher
								L PHG	Higher
								B ACC	Higher
								L Cingulate Gyrus	Higher
								B Cuneus	Lower

Abbreviations: Ant = anterior, B = bilateral, CT = cluster threshold, CDRS = children's depression rating scale, CDT = cluster determining threshold, Comm = community, FDR = false discovery rate, FWE = family-wise error, GC = Granger causality, GRF = gaussian random field, HC = healthy controls, k = cluster extent, L = left, MC = Monte Carlo simulations, MDD = major depressive disorder, NR = not reported, Post = posterior, PPI = psychophysiological interaction, R = right, ROI = region of interest, SVC = small volume correction, T = time, WB = whole brain

Brain regions: ACC = anterior cingulate cortex, ACG = anterior cingulate gyrus, AI = Ant. Insula, AMG = amygdala, AMIC = anterior middle insular cortex, dACC = dorsal ACC, dlPFC = dorsolateral prefrontal cortex, DMN = default mode network, dmPFC = dorsomedial PFC, HPC = hippocampus, IFG = inferior frontal gyrus, IPL = inferior parietal lobule, ITG = inferior temporal gyrus, LOC = lateral occipital cortex, lPFC = lateral PFC, MFG = middle frontal gyrus, mOFC = medial OFC, mPFC = medial PFC, MTG = middle temporal gyrus, NAcc = nucleus accumbens, OC = occipital cortex, OFC = orbitofrontal cortex, PAG = periacqueductal gray, PCC = posterior cingulate cortex, PCG = paracingulate gyrus, PFC = prefrontal cortex, pgACC = perigenual ACC, PHG = parahippocampal gyrus, postCG = postcentral gyrus, preCG = precentral gyrus, rACC = rostral ACC, SC = sensory cortex, sgACC = subgenual ACC, SFG = superior frontal gyrus, SMA = supplementary motor area, SMG = supramarginal gyrus, STC = superior temporal cortex, STG = superior temporal gyrus, STL = superior temporal lobe, supragACC = supragenual ACC, vmPFC = ventromedial PFC, vlPFC = ventrolateral PFC, VS = ventral striatum, vPFC = ventral PFC, VTA = ventral tegmental area

* negative correlation with depressive scores.

** positive correlation with depressive scores.

*** Functional connectivity correlated with depressive scores.

reactivity/modulation in depression, including amygdala hyperactivity to negative emotional stimuli. Alterations in automatic regulatory prefrontal regions (ER3; rACC/vmPFC) were noted for negative and positive stimuli, but the direction of activation (hyper vs. hypo) was inconsistent.

4.4.1.2. Behavioral control. Our search yielded nine studies that utilized behavioral control paradigms in youth depression, two of which were not included in the aggregate data synthesis due to the methods being unsuitable for comparison (Engels et al., 2010; Stange et al., 2018) but were included in the tables for the sake of completeness (Table 4). Engels

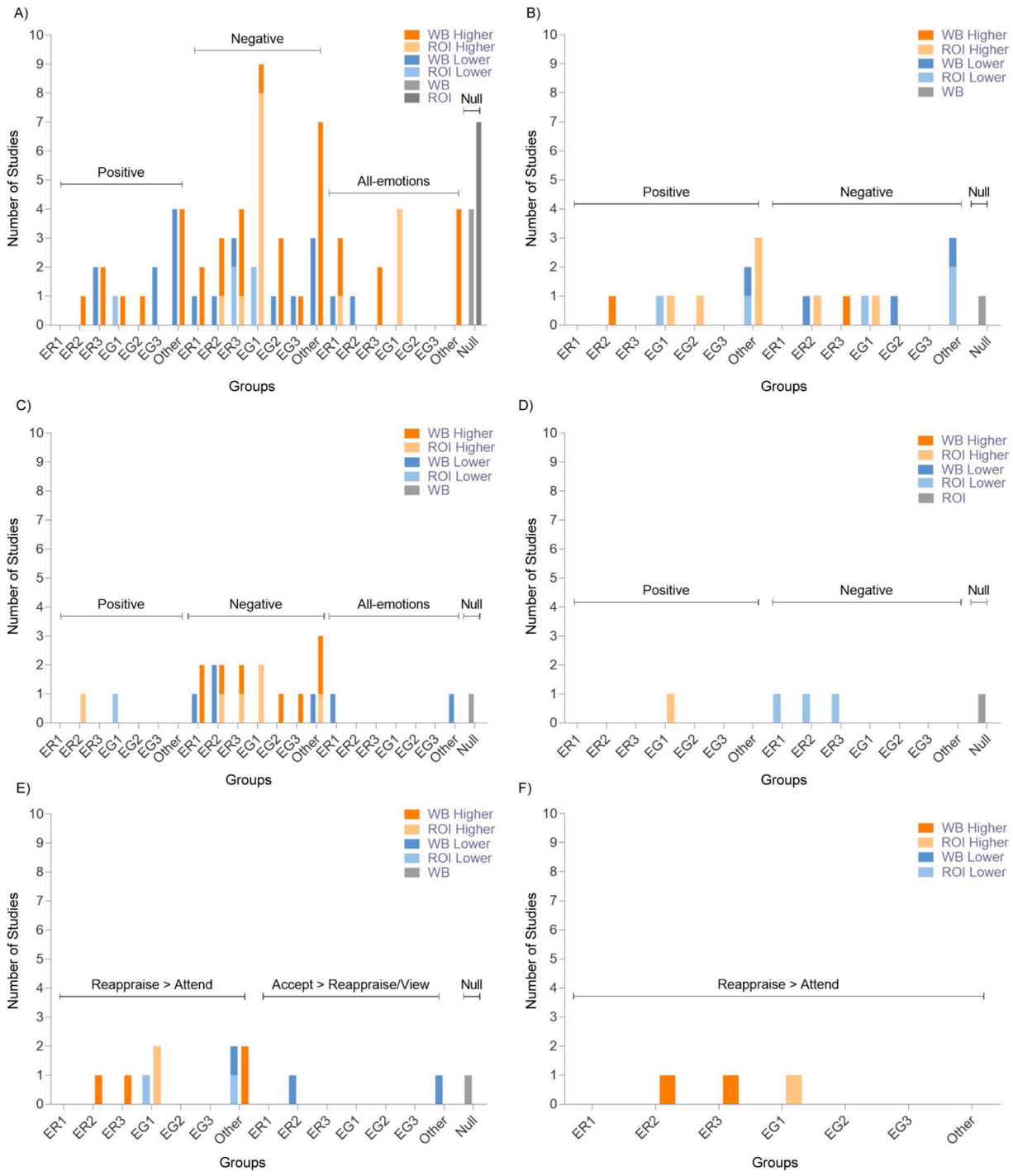

Fig. 2. Stacked histograms illustrating the number of studies that showed depression (A,C,E) and substance use (B,D,F) associated aberrant activation of EG1 (amygdala), EG2 (insula), EG3 (basal ganglia), ER1 (dmPFC/dACC/SMA/Pre-SMA), ER2 (dlPFC/vlPFC/lOFC), ER3 (rACC/vmPFC/mOFC/hippocampus) and other regions in **A,B)** tasks of affective reactivity and modulation for positive, negative and all emotion (all-emotions) contrasts in depression (**A**) and substance use (**B**). **C, D**) behavioral control for positive and negative emotions in depression (**C**) and substance use (**D**) and **E, F**) cognitive modulation (reappraisal and acceptance) of negative affect in depression (**E**) and substance use (**F**).

et al. (2010) did not analyze group differences between depressed individuals and healthy controls and instead studied interaction effects of different types of anxiety and anhedonic depression on brain activation, and Stange et al. (2018) applied a modelling approach which could not be integrated into our data synthesis.

A few studies reported altered amygdala activation in depressed youth relative to healthy controls. Two studies found exaggerated amygdala activity to negative distractors (de Bellis and Hooper, 2012; Greening et al., 2013), and one found lower activity to positive distractors (Greening et al., 2013). Two studies found increased depression-associated activation of ER2 regions (specifically dlPFC) in response to negatively valanced distractors (Colich et al., 2017; de Bellis and Hooper, 2012); however, there were some opposing findings. For instance, Greening et al. (2013) found hypoactivation of ER1 regions (dmPFC) in depressed youth in response to negative distractors, whereas (Kaiser et al., 2015) found hyperactivation of ER1 regions (dACC) in

Table 3
PPI findings in affective reactivity/modulation paradigms.

Positive		Negative		All Emotions	
Higher					
Insula	ER1	Amygdala	ER2	mPFC	Other
Insula	ER2	sgACC	EG2	Amygdala	ER3
Insula	EG1	sgACC	Other		
Insula	Other				
Lower					
dlPFC	ER2	ACC	EG2	Amygdala	ER2
		Amygdala	ER2	Amygdala	ER3
		Insula	Other	Amygdala	Other

Abbreviations: ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; sgACC = subgenual ACC.

depressed youth to negative distractors (Fig. 2C).

4.4.1.3. Cognitive modulation. Our search yielded six studies that utilized cognitive modulation paradigms that required the reappraisal or acceptance of negative affect (Table 5, Fig. 2E). Amygdala activation was found to be both increased (Greening et al., 2014) and decreased (Perlman et al., 2012) during emotional reappraisal in depressed youth relative to healthy controls. Emotion regulatory regions (vlPFC, dlPFC, mPFC) were found to be hyperactive during reappraisal in depressed youth in two studies (Perlman et al., 2012; Stephanou et al., 2017), but hypoactive for acceptance (a mindfulness strategy wherein subjects are instructed to actively be aware of their emotion state but not attempt to modify their emotional response (Smoski et al., 2015) in depressed youth relative to healthy controls. On the other hand, LeWinn et al. (2018) found no group differences in brain activity during reappraisal, instead they reported a group-by-reappraisal success interaction, such that increased activity in the dmPFC and dlPFC was associated with greater reappraisal success in controls but not in depressed youth.

PPI analyses revealed altered connectivity between the amygdala and cortical regions (Perlman et al., 2012; Platt et al., 2015), and between the dmPFC and the anterior insula during reappraisal (LeWinn et al., 2018), in depressed compared to healthy youth. Specifically, Perlman et al. (2012) reported decreased functional connectivity between the amygdala and several ER regions (vlPFC, dlPFC) while depressed youth maintained negative emotion, and increased connectivity between the amygdala and the dlPFC and sgACC while depressed youth attempted to reappraise negative affect (Perlman et al., 2012). Studies also showed altered connectivity between other regions during reappraisal, specifically between the frontal pole and several regions, including the amygdala, caudate, dlPFC, and HPC (Platt et al., 2015).

In summary, there were few consistent findings for behavioral control/cognitive modulation in depression; the only discernable pattern was increased emotion regulatory structure activation during control/modulation of negative emotional stimuli.

4.4.1.4. Resting state functional connectivity. Of the 26 rsFC studies included in this review, 19 used the amygdala as a seed region. Other brain structures that were frequently used as seeds include cingulate regions (sgACC, pgACC, dACC, PCC), basal ganglia (Striatum, NAcc) and dmPFC (Table 6; Figs. 3 and 4).

Most studies that used the amygdala as a seed region reported altered amygdala-seeded functional connectivity in depressed youth (Figs. 3, 4). The most consistent finding was lower functional connectivity between the amygdala and prefrontal structures, largely in the ER2 (lPFC) and ER3 (rACC/vmPFC) regions in depressed youth (n = 14); however, there were also a number of inconsistent findings. For example, five studies found increased connectivity between the amygdala and ER2/ER3 (lPFC/rACC/vmPFC) structures in depression, and four studies reported no group differences. There were also several instances of opposing findings. For example, Pannekoek et al. (2015) found increased rsFC (lower negative coupling) between the amygdala and the pgACC in depressed youth, whereas Rzepa and McCabe (2016) found reduced rsFC between the same two regions. Studies also found altered cortico-subcortical connectivity using other seeds (Anand et al., 2009; Cullen et al., 2009; Fischer et al., 2018; Gabbay et al., 2013; Rzepa and McCabe, 2016, 2018); however, there appears to be very little agreement on implicated regions and the direction of alteration between studies when seeds other than the amygdala were used.

4.4.1.4.1. Longitudinal studies. Three studies were identified that investigated changes in functional connectivity over time in relation to depression. Methods used were contrasting, and seed-based connectivity analyses did not result in consistent findings across studies. Studies reported: 1) significant increase in amygdala–sgACC connectivity from mid- to late-adolescence in participants who developed MDD, relative to those who did not (Davey et al., 2015), 2) increased functional connectivity in centromedial amygdala-rACC was found to be associated with increased depression in adulthood, but not in childhood (Jalbrzikowski et al., 2017), and 3) decreased sgACC connectivity with dmPFC, PCC, angular gyrus, and middle temporal gyrus from mid- to late-adolescence associated with higher depressive symptoms during late adolescence (Strikwerda-Brown et al., 2015).

In summary, several studies reported lower functional connectivity between the amygdala and top-down regulatory prefrontal (ER2 and ER3; lPFC/rACC/vmPFC) and other regions to be associated with depression. Some studies used other seeds, but these revealed no discernable patterns.

4.4.2. Substance Use/Abuse/Dependence

4.4.2.1. Affective reactivity and affective modulation. For this dimension, our search yielded eight studies (Table 7). Studies found altered substance use-associated activation of both emotion generating/processing and emotion regulating regions; however, there was little consistency in regions implicated and direction of results (Fig. 2B). The only consistent finding was higher activation of the lPFC (ER2) in response to positive cues (found in two studies: Heitzeg et al., 2015; Schuckit et al., 2016) in substance using youth. There were some opposing findings, such as higher and lower substance use-associated activation of the amygdala (Gruber et al., 2009; Heitzeg et al., 2015; Spechler et al., 2015) (Fig. 2B).

Two studies (Cyders et al., 2014; Nikolova et al., 2016) did not perform standard task activation analysis in substance using youth. Nikolova et al. (2016) demonstrated that a greater mismatch between ventral striatum and amygdala reactivity was predictive of problem drinking. Cyders et al. (2014) found that negative urgency (the tendency to act rashly when distressed) predicted increased activation in the vmPFC in response to alcoholic odors in individuals who had indulged in at least one binge in the last month.

4.4.2.2. Behavioral control. Our search yielded two studies that utilized behavioral control paradigms in substance using youth (Table 8; Fig. 2D). Aloi et al. (2018) used an affective Stroop task and found that Alcohol Use Disorders Identification Test (AUDIT) scores correlated with amygdala activation for positive > negative and positive > neutral contrasts. Aloi et al. (2018) also reported a negative correlation between AUDIT scores and activation in the dlPFC, dmPFC, PCC, precuneus, and ACC for incongruent > congruent trials and a positive correlation between Cannabis Use Disorders Identification Test (CUDIT) scores and activation in the PCC, precuneus, and inferior parietal lobule (Aloi et al., 2018). In addition, the study reported amygdala hyper-responsiveness to negative stimuli in participants with high AUDIT scores (when CUDIT scores were also high). Cohen-Gilbert et al. (2017) utilized an emotional Go/No-Go task and found that high recent binge drinking was correlated with decreased activity in ER1/ER2 regions (dlPFC, dmPFC) during negative vs neutral inhibitory trials.

Table 4
Depression associated activation during behavioral control paradigms.

Study	Methodological aspects					Significant findings			
	No. of subjects (females)	Mean Age	Age-range	Task	Statistical Threshold and analysis method	ROI for activation analysis	Contrast	Regions	Recruitment/ connectivity in DEP vs HC
Chuang et al. (2016)	MDD = 82 (82 F)	15.72	13.7-17.97	Affective Go/No-Go	ROI CT FWE $p < 0.05$ CDT $Z > 2.3$	OFC	Happy > neutral distractors	OFC	Higher
Colich et al. (2016)	MDD = 18 (15 F)	15.61	12-17	Affective Go/No-Go	WB CT $p < 0.05$ CDT $Z > 2.0$	WB	Sad no-go > happy no-go	dlPFC	Lower
								Occipital Cortex	Lower
							Sad no-go	Occipital Cortex	Lower
Colich et al. (2017)	MDD = 18 (16 F)	15.44	12-17	Emotional distractor task	WB CT $p < 0.05$ (GRF) CDT $Z > 2.0$	WB	Fearful > neutral distractors	dACC	Lower
								R IFG/MFG	Lower
								L LOC	Lower
								R LOC/SPL	Lower
							Ignoring neutral faces	dACC	Lower
								R LOC/SPL	Lower
de Bellis and Hooper, 2012	Maltreated youth with depression = 5 (3 F)	15.5	11.6-18.1	Emotion oddball task	WB and ROI CDT $p < 0.001$, $k >= 5$	AMG, MFG	Target > neutral	L MFG	Lower
								R preCG	Lower
								L sgACC	Higher
							Sad > neutral distractors	L IFG	Higher
								R MTG	Higher
								AMG	Higher
Engels et al. (2010)	Anhedonic depression (AD) and anxiety = 91 (51 F)	19.01	NR	Emotion word Stroop task	ROI CT FWE $p < .05$ k by MC CDT $p = 0.03/0.04$	dlPFC, occipital cortex, IFG, ACC, AMG	Negative-neutral contrast	Increased AD was associated with decreased R dlPFC activation at low levels of anxious arousal (AAr) but increased right dlPFC activation at high levels of AAr. Increased AD was associated with decreased right LOC activation at low levels of anxious apprehension (AAp), but with increased right LOC activation at high levels of AAp. Increased AD was also associated with decreased activation in the right IFG when combined with low AAp and high AAr. Bilateral AMG activation was correlated with both AD and AAr. AD captured unique variance in the dACC and rostral ACC.	
Greening et al. (2013)	MDD = 18 (12 F)	26.1	16-59	Mixed-emotions task (target/distracters), happy/neutral (HN), fearful/neutral (FN), neutral/happy (NH) and neutral/fearful (NF)	ROI and WB ROI: CT $p < 0.05$, SVC $k > 5$, CDT $p < 0.01$ WB: CT FWE $p < 0.05$ $k > 30$, CDT $p < 0.005$	AMG	FN	R AMG	Higher
							HN	R AMG	Lower
							NH	L AMG	Lower
								dmPFC	Lower
							NF	L vlPFC	Lower
Kaiser et al. (2015)	Total sample = 92 (53 F), 6% current MDD, 26% past MDD, 2% dysthymic	19.03	18-25	Emotion word Stroop task (contrasted with color-word Stroop task)	WB, ROI for PPI CT FWE $p < 0.05$ k by MC CDT $p < 0.01$	WB	Negative distractors	dACC*	Higher

(*continued on next page*)

Table 4 (*continued*)

Study	Methodological aspects					Significant findings			
	No. of subjects (females)	Mean Age	Age-range	Task	Statistical Threshold and analysis method	ROI for activation analysis	Contrast	Regions	Recruitment/ connectivity in DEP vs HC
								Brain stem	Higher
								Caudate	Higher
								L Thalamus	Higher
								PCC	Higher
								PHG	Higher
							Negative > neutral distractors	dACC - PCC (PPI)*	Higher
Stange et al. (2018)	remitted MDD = 43 (65% female)	21.4	18-23	Cold cognition: parametric Go/No-Go. Hot cognition: The facial emotion perception task (FEPT).	ROI CT $p < 0.05$ k by < C CDT $p < 0.005$	SEN and CCN masks	Main effect of group on CCN: HCs demonstrated greater activation than individuals with rMDD in the left MFG across both conditions. Two factorial models in SPM8: sadness/rejections and fear/rejections. Sadness and rejections model: During rejections, HCs demonstrated greater activation in these CCN regions than individuals with rMDD. While identifying sad faces, rMDD showed greater activation in CCN regions than HCs. Fear and rejections model: HCs showed higher activation in the bilateral IPL than rMDD. HCs had greater deactivation in the same regions compared to rMDD. Group x condition contrast in the SEN: including the SMG and MTG.		
Szekely et al. (2017)	Total sample = 27, high anhedonic depression = 9	19.44	NR	Emotion word Stroop task	ROI for PPI CT $p < 0.05$ k by MC	dACC for PPI	Unpleasant vs neutral words	No depression associated group differences reported	

Abbreviations: Ant = anterior, AUD = alcohol use disorder, B = bilateral, Comm = community, CT = cluster threshold, CDT = cluster determining threshold, FDR = false discovery rate, FWE = family-wise error, HC = healthy controls, k = cluster extent, L = left, MC = Monte Carlo simulations, MJ = marijuana, NR = not reported, PPI = psychophysiological interaction, R = right, ROI = region of interest, rsFC = resting state functional connectivity, SVC = small volume correction, T = time, WB = whole brain.

Brain regions: ACC = anterior cingulate cortex, AMG = amygdala, CCN = cognitive control network, dACC = dorsal ACC, dlPFC = dorsolateral prefrontal cortex, DMN = default mode network, dmPFC = dorsomedial PFC, LOC = lateral occipital cortex, IFG = inferior frontal gyrus, IPL = inferior parietal lobule, MFG = middle frontal gyrus, MTG = middle temporal gyrus, NAcc = nucleus accumbens, OFC = orbitofrontal cortex, PCC = posterior cingulate cortex, PHG = parahippocampal gyrus, PFC = prefrontal cortex, preCG = precentral gyrus, SEN = salience and emotion network, sgACC = subgenual ACC, SFG = superior frontal gyrus, SPL = superior parietal lobule, vlPFC = ventrolateral PFC,

* correlated with depressive symptoms.

Table 5
Cognitive modulation paradigms in youth depression.

Study	Methodological aspects						Significant findings		
	No. of subjects	Mean Age	Age-range	Task	Statistical Threshold and analysis method	ROI for activation analysis	Contrast	Regions	Recruitment/ connectivity in DEP vs HC
Greening et al. (2014)	MDD = 19 (13 F)	26.8	16-59	Cognitive reappraisal task	WB and ROI ROI: CDT $p < 0.01$ $k > 10$ WB: CT FWE $p < 0.05$ $k > 47$ CDT $p < 0.005$	AMG	Sad scenes	Ant vlPFC	Lower
								L Lingual Gyrus	Higher
							Reappraise > maintain	R postCG	Higher
								R IPL	Higher
								AMG	Higher
							Positive scenes	dlPFC	Higher
								SMA	Higher
LeWinn et al. (2018)	MDD = 41 (28 F)	16.1	13-17	Cognitive reappraisal task	WB, ROI and ROI for PPI CT $p < 0.05$ k by 3dClustSim CDT $p < 0.01$	AMG	Reappraise > maintain	No group differences in activation reported Group*reappraisal success interaction reported in the dmPFC and dlPFC; greater activation was associated with higher reappraisal success in controls but depressed adolescents	
						dmPFC, dlPFC for PPI	Reappraisal	dmPFC - Ant Insula	Lower
Perlman et al. (2012)	MDD = 14 (6 F)	15.7	13-17	Cognitive reappraisal task	WB, ROI and ROI for PPI WB: CT $p < 0.05$ k by AlphaSim ROI: CT $p < 0.05$ $k = 3$	AMG	Maintain > reappraise	R Mid OC	Higher
								B Lingual Gyrus	Higher
								L IFG	Lower
								R AMG	Higher
							Maintain	AMG - B insula, B ventral MFG, R superior frontal, L STG, R IFG, MTG (PPI)	Lower
							Reappraise	L MFG - sgACC	Higher
Platt et al. (2015)	MDD = 15 (13 F)	15.2	15-17	Cognitive reappraisal of peer rejection using the chatroom paradigm	WB, ROI for PPI CT FDR $p < 0.001$ k by AlphaSim CDT $Z > 2.3$	Frontal pole for PPI	Reappraise > maintain	No group differences in activation reported	
							Reappraise > maintain	Frontal pole - Cerebellum, fusiform gyrus, PHG, HPC, caudate, thalamus, AMG, R IPL, B MTG, B Parietal lobe, R MFG, L SFG (PPI)	Higher
Smoski et al. (2015)	remitted MDD = 18 (14 F)	24.5	19-55	Emotion regulation task with one of two strategies: accept and reappraise	WB and ROI CT $p < 0.05$ k by MC CDT $p < 0.005$	AMG, Frontal Pole	Accept > view	R Frontal Pole	Lower
							Accept > reappraise	R PCG	
								R MFG	Lower
Stephanou et al. (2017)	MDD = 53 (31 F)	19.72	15-25	Cognitive reappraisal task	WB and ROI ROI: CT FWE-SVC $p < 0.05$ WB: CDT $p < 0.001$, $k > 10$	AMG	reappraise > look	mPFC	Higher
								lPFC	Higher
								vmPFC	Higher
								Fusiform	Higher
								ParaHPC	Higher
								Cerebellum	Higher
								preSMA	Lower
							Look > reappraise	AMG	Lower

Abbreviations: Ant = anterior, B = bilateral, Comm = community, CT = cluster threshold, CDT = cluster determining threshold, DEP = depressed youth, FDR = false discovery rate, FWE = family-wise error, HC = healthy controls, k = cluster extent, L = left, MC = Monte Carlo simulations, NR = not reported, PPI = psycho-physiological interaction, R = right, ROI = region of interest, SVC = small volume correction, T = time, WB = whole brain
Brain regions: ACC = anterior cingulate cortex, AMG = amygdala, dACC = dorsal ACC, dlPFC = dorsolateral prefrontal cortex, DMN = default mode network, dmPFC = dorsomedial PFC, FPC = frontopolar cortex, FPN = frontoparietal network, HPC = hippocampus, ICA = independent component analysis, IFG = inferior frontal gyrus, IPL = inferior parietal lobule, lPFC = lateral PFC, MFG = middle frontal gyrus, mOFC = medial OFC, mPFC = medial PFC, MTG = middle temporal gyrus, NAcc = nucleus accumbens, OC = occipital cortex, OFC = orbitofrontal cortex, PCC = posterior cingulate cortex, PCG = paracingulate gyrus, PFC = prefrontal cortex, PHG = parahippocampal gyrus, postCG = postcentral gyrus, preCG = precentral gyrus, sgACC = subgenual ACC, SFG = superior frontal gyrus, SMA = supplementary motor area, STG = superior temporal gyrus, vmPFC = ventromedial PFC, vlPFC = ventrolateral PFC, VTA = ventral tegmental area

4.4.2.3. Cognitive modulation. Our search yielded one study for this dimension (Table 9; Fig. 2F). Zimmermann et al. (2017) found that reappraisal success was lower and amygdala (EG1) activity during reappraisal was higher in cannabis users. They also found higher activity in the precentral gyrus, superior frontal gyrus (SFG), and SMA during the reappraisal of negative emotions. In addition, this study demonstrated lower connectivity between the amygdala and the dlPFC during cognitive reappraisal in cannabis users compared to non-users.

In summary, the number of studies in substance use disorders were relatively few, and no consistent patterns emerged for affective reactivity/modulation paradigms. However, lower activity of prefrontal structures in behavioral control studies of substance use is inconsistent with depression, while increased activity of prefrontal structures in studies of cognitive modulation in substance use is consistent with studies on depression.

4.4.2.4. Resting state functional connectivity. Our search yielded 13 resting-state studies in substance using youth. Altered cortico-subcortical connectivity was reported frequently by studies on substance using youth (Table 10; Fig. 3, 4). Several studies reported lower rsFC between the amygdala and the mOFC (ER3) in substance users (Crane et al., 2018; Peters et al., 2015, 2017) vs non-users. Altered

Table 6
Depression-associated aberrant resting state functional connectivity.

Study	Methodological aspects					Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Statistical Threshold and analysis method	Seeds for connectivity analysis	Seed	Target	Connectivity in DEP vs HC
Altinay et al. (2016)	MDD = 15 (9 F)	27	18-60	Seed to voxel CT p < 0.01 k by 3dclustsim CDT p < 0.05	AMG	L AMG	Cerebellum	Lower
						L AMG	Lingual gyrus	Lower
						L AMG	Middle occipital gyrus	Lower
						R AMG	Inferior, middle and orbital FC	Lower
Anand et al. (2009)	MDD = 15 (11 F)	29	18-60	Seed to AMG, PST, DMTHAL CT?	pgACC	pgACC	B DMTHAL	Lower
						pgACC	L PST	Lower
Bebko et al. (2015)	Total Sample (LAMS youth) = 42 (18 F), (MDD = 12)	14.32	9.9-17.7	Seed to mask P < 0.005 CDT, P < 0.05 CT with AlphaSim	AMG to mask including, striatum, PFC, mPFC, OFC, vlPFC, dACC, insula	AMG	R posterior insula[1]	Lower
Hirshfeld-Becker et al., 2019)	MDD = 10 (7 F) (from non MDD at T1, 10 converted (CTV))	11.5	8-14	Seed to voxel CT FDR p <?, Bonferroni corrected CDT p < 0.001	DMN (mean of dmPFC, PCC), dlPFC, sgACC, AMG		No group differences between CTV and HC reported	
Burghy et al. (2012)	Comm. Sample (Wisconsin Study of Families and Work) = 57 (28 F)	18.44	12-17	Seed to voxel CT p < 0.05, k by 3dClustStim and 3dFWHMx, CDT NR	AMG	AMG	vmPFC[2]	Higher
Callaghan et al. (2017)	Total sample = 129, MDD = 14	16.46 for rs-MRI, 18.7 for first onset MDD	NR	Seed to voxel FWE corrected (GRF), CDT p < 0.001	AMG, NAcc, VS	AMG	Whole AMG and CM AMG - temporal and insular cortex connectivity at age 16 mediated the relationship between maternal aggression and MDD onset at age 19	
Connolly et al. (2017)	MDD = 48 (29 F)	16.1	12-19	Seed to voxel CT p < 0.025 k by MC, CDP p < 0.05	AMG	R AMG	B dlPFC	Lower
						R AMG	B vlPFC	Lower
						R AMG	B vmPFC	Lower
						L AMG	L dlPFC	Lower
						L AMG	L vmPFC	Lower
						Greater baseline positive connectivity between the right AMG and the orbital MFG was associated with higher CDRS score at follow up.		
Cullen et al. (2009)	MDD = 12 (9 F)	16.5	12-19	Seed to voxel GRF, Z > 2.3 CT p < 0.05	sgACC, AMG, supragACC	sgACC	supragACC	Lower
						sgACC	R mFC	Lower
						sgACC	L sFC	Lower
						sgACC	L iFC	Lower
						sgACC	L STC	Lower
						sgACC	Insula	Lower
Cullen et al. (2014)	MDD = 41 (32 F)	15.7	12-19	Seed to voxel GRF, Z > 2.3 CT p < 0.05	AMG	AMG	L HPC	Lower
						AMG	paraHPC	Lower
						AMG	OFC	Lower
						AMG	Temporal pole	Lower
						AMG	B Precuneus	Higher
Davey et al. (2015)	Total sample = 56(25 F), MDD = 8(4 F)	16.5 at T3 and 18.8 at T4	T3: 15-17, T4: 18-20	Seed to voxel and mask of sgACC CT FWE p < 0.05 k by MC	AMG	AMG	sgACC[3]	Higher
						AMG	L OFC[4]	Higher
						AMG	B Precuneus	Higher
DeWitt et al. (2017)	MDD = 14 (11 F)	16.68	12-19	Seed to voxel CT FWE p < 0.05 k = 41 CDT p < 0.001	dACC, sgACC, NAcc, pgACC		No group differences reported	
Fischer et al. (2018)	Converted MDD (CTV) - 20 F, did not develop depression (RES) - 20 F	18.9	NR	Seed to voxel CT FDR p < 0.05 (GRF) CDT p < 0.001	AMG, Ant Insula, dlPFC	R Ant Insula	DMTHAL	Higher (CTV > HC)
						R Ant Insula	Lower STG	Higher (CTV > HC)
Gabbay et al. (2013)	MDD = 21 (12 F)	17.1	12-19	Seed to voxel GRF, Z > 2.3 CT p < 0.008	NAcc, Caudate, Putamen	Caudate	sgACC	Higher
						Caudate	pgACC	Higher
						Caudate	STL	Lower
						Caudate	PCG	Lower
						Putamen	PCG	Higher
						Putamen	IFG	Higher
						NAcc	MTG	Lower
Geng et al. (2016)	MDD = 26 (19 F)	15.6	13-17	Seed to PFC mask CT p < 0.05 with AlphaSim k > 48 CDT p > 0.05	HPC	HPC	B vPFC	Lower
						HPC	B dlPFC	Lower
Jacobs et al. (2016)	remitted MDD (rMDD) = 34 (25 F), active	rMDD = 21.06,	18-25	Seed to voxel CT p < 0.05 k by MC CDT p < 0.001	PCC, AMG, sgACC	L PCC	R MFG	Higher (All MDD (positive connectivity) > HC

(continued on next page)

Table 6 (*continued*)

Study	Methodological aspects					Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Statistical Threshold and analysis method	Seeds for connectivity analysis	Seed	Target	Connectivity in DEP vs HC
	MDD (aMDD) = 17 (11 F)	aMDD = 22.35				AMG	R Ant Insula/ Caudate	(negative connectivity) Higher (All MDD (positive connectivity) > HC (negative connectivity)
Jalbrzikowski et al. (2017)	Community longitudinal sample of 157 and cross-sectional sample of 89	NR	10-22, 20-25	Seed to voxel CT p < 0.05 k by MC CDT p < 0.001	vmPFC, BL and CM AMG	Higher functional connectivity in CM amygdala-rACC was associated with increased anxiety and depression in adulthood, but not in childhood.		
Jenkins et al. (2017)	rMDD = 32 (22 F)	21.48	18-23	Seed to voxel CT NR k by MC CDT p < 0.001	AMG, Ant Insula, sgACC	No group differences reported		
Kim et al. (2015)	MDD = 22 (8 F)	13.9	13-18	Seed to voxel CT FWE p < 0.05 k by MC CDT p < 0.001	AMG, PCC	AMG AMG AMG PCC PCC PCC R AMG R HPC R HPC	R subcallosal R PHG R OFC[1] L preCG L Insula L Parietal Lobule[1] R SFG R Insula R MFG	Lower Lower Lower Higher Higher Higher Lower Lower Lower
Lee at al. (2019)	MDD = 23 (14 F)	15.4	13-18	Seed to voxel CT p < 0.05 CDT p < 0.001 FDR corrected results reported	AMG, dACC, sgACC, ant Insula, post Insula, middle Insula, HPC	L mid Insula L mid Insula L post Insula R dACC	B MFG R SFG R Frontal Pole L Insula	Higher Higher Higher Higher
Pannekoek et al. (2015)	MDD = 26 (23 F)	15.4	12-21	Seed to voxel CT p < 0.05 CDT Z > 2.3	AMG, dACC, PCC	L AMG L AMG L AMG L AMG R AMG R AMG R AMG R AMG R AMG R AMG	R MFG R IFG R preCG R postCG L Frontal pole R pgACC R PCG R SFG L Angular Gyrus L LOC L SMG	Higher Higher Higher Higher Decreased negative Decreased negative Decreased negative Decreased negative Decreased negative Decreased negative Decreased negative
Rzepa and McCabe (2016)	Depressive symptomatology (high risk group) = 17 (13 F)	16.59	13-18	Seed to voxel CT FWE p < 0.05 CDT Z > 2.3 Bonferroni correction reported p < 0.016	AMG, dmPFC, pgACC	dACC dACC dACC AMG L AMG L AMG R AMG pgACC pgACC pgACC R dmPFC R dmPFC R dmPFC R dmPFC	R MFG R Frontal Pole R IFG pgACC Precuneus PCC HPC Thalamus Pallidum Putamen Precuneus LOC Frontal pole ACC/ paracingulate	Lower Lower Lower Lower Lower Lower Lower Lower Lower Lower Lower Lower Higher Higher
Rzepa and McCabe (2018)	Depressive symptomatology = 44 (34 F)	18.09	13-21	Seed to voxel CT FWE p < 0.05 CDT Z > 2.3 Bonferroni correction reported p < 0.016	NAcc, dmPFC, pgACC	L dmPFC L NAcc pgACC pgACC pgACC pgACC pgACC R dmPFC R dmPFC pgACC pgACC	postCG Precuneus Thalamus Putamen Caudate Planum temporale STG ITG/MTG LOC SFG/MFG postCG	Higher Higher Higher Higher Higher Higher Higher Lower Lower Lower Lower
Scheuer et al. (2017)	Developed depressive symptoms in the future post-scan = 18 (10 F)	13.51	12-16	Seed to voxel 2 levels of correction with MC: CT p < 0.05, p <	AMG	R AMG R AMG R AMG L AMG	L IFG L SMG R midcingulate	Lower Lower Lower Lower

(*continued on next page*)

Table 6 (*continued*)

Study	Methodological aspects					Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Statistical Threshold and analysis method	Seeds for connectivity analysis	Seed	Target	Connectivity in DEP vs HC
Schwartz et al. (2019)	MDD = 41 (26 F)	26.01	18-35	0.01 CDT Z > 2.25, Z > 3.00 Seed to voxel CT p < 0.05 k > = 317 CDT p < 0.001	sgACC		L cerebellar vermis	
						R sgACC	pgACC	Lower
						R sgACC	dACC	Lower
Strikwerda-Brown et al. (2015)	T1 total sample = 72 (33 F), T2 total sample = 56 (26 F)	T1 = 16.47, T2 = 18.75	NR	Seed to voxel CT FWE p < 0.05 k by MC CDT p < 0.01	sgACC	sgACC	PCC[5]	Lower at T1
						sgACC	R dPFC	Lower at T1
						sgACC	R Angular Gyrus	Lower at T1
						sgACC	dmPFC[6]	Lower at T2
						sgACC	vmPFC	Lower at T2
						Change in connectivity between the sgACC and the PCC, R angular gyrus, dmPFC and vmPFC from T1 to T2 was negatively correlated to depressive scores at T2		
Zhang et al. (2014)	MDD = 32 (18 F)	20.53	18-24	Seed to voxel CT FWE p < 0.05 k > = 50 CDT p < 0.001	AMG	L AMG	L OFC	Higher negative

Abbreviations: Ant = anterior, B = bilateral, CT = cluster threshold, CDRS = children's depression rating scale, CDT = cluster determining threshold, Comm = community, FDR = false discovery rate, FWE = family-wise error, GRF = gaussian random field, HC = healthy controls, k = cluster extent, L = left, MC = Monte Carlo simulations, MDD = major depressive disorder, NR = not reported, PPI = psychophysiological interaction, R = right, ROI = region of interest, rs-MRI = resting state MRI, rsFC = resting state functional connectivity, SVC = small volume correction, T = time, WB = whole brain

Brain regions: ACC = anterior cingulate cortex, AMG = amygdala, BL = basolateral, CM = centromedial, dACC = dorsal ACC, dlPFC = dorsolateral prefrontal cortex, DMN = default mode network, dmPFC = dorsomedial PFC, DMTHAL = dorsomedial thalamus, FPC = frontopolar cortex, FPN = frontoparietal network, HPC = hippocampus, iFC = inferior frontal cortex, IFG = inferior frontal gyrus, IPL = inferior parietal lobule, ITG = inferior temporal gyrus, LOC = lateral occipital cortex, lPFC = lateral PFC, MFG = middle frontal gyrus, mFC = middle frontal cortex, mOFC = medial OFC, mPFC = medial PFC, MTG = middle temporal gyrus, NAcc = nucleus accumbens, OC = occipital cortex, OFC = orbitofrontal cortex, PCC = posterior cingulate cortex, PCG = paracingulate gyrus, PFC = prefrontal cortex, pgACC = perigenual ACC, PHG = parahippocampal gyrus, postCG = postcentral gyrus, preCG = precentral gyrus, PST = pallidostriatum, rACC = rostral ACC, sgACC = subgenual ACC, sFC = superior frontal cortex, SFG = superior frontal gyrus, SMA = supplementary motor area, SMG = supramarginal gyrus, STC = superior temporal cortex, STG = superior temporal gyrus, STL = superior temporal lobe, supragACC = supragenual ACC, vmPFC = ventromedial PFC, vlPFC = ventrolateral PFC, VS = ventral striatum, vPFC = ventral PFC, VTA = ventral tegmental area.

[1]negatively correlated with depressive symptoms.
[2]correlated with depressive symptoms for females.
[3]higher in those that developed MDD at T4.
[4]correlated with negative affect.
[5]positively correlated with depressive symptoms.
[6]correlated with depressive symptoms at T1.
[7]negatively correlated with depressive symptoms at T2.

cortico-subcortical connectivity in substance users was also shown with caudate, NAcc, mOFC, and ACC seeds (Huang et al., 2014; Posner et al., 2016; Yuan et al., 2016; Zimmermann et al., 2018); however, there were some inconsistencies. For example, Manza et al. (2018) found no group differences in NAcc connectivity. In addition, Weissman et al. (2015) showed that stronger cortico-subcortex connectivity was associated with earlier onset of substance use. These findings were replicated using an ICA approach. Lee and Telzer (2016) showed that decreased negative coupling between the cortical and subcortical systems was associated with earlier onset of substance use; however this finding was not included in our quantitative analysis because ICA methods are not directly comparable to seed based methods.

In summary, there was marked variability in seed regions used by substance use/SUD studies. The only discernible pattern was lower connectivity of the amygdala to the OFC.

5. Discussion

In the context of affect dysregulation, "dual systems" or "mismatch" models have been implicated in the development of both depression (Nelson et al., 2005) and substance use (Casey and Jones, 2010) in youth. The aim of this review was to explore the extant literature to examine and compare the underlying neural circuitry of emotion regulation in depressed and substance using youth, using both task-based, and rsFC studies focusing on emotion processing and regulation circuitry. The goal was thus to make inferences about the validity of the dual systems model for depression and substance use/abuse/dependence based on the existing literature, and subsequently identify and discuss the relevant themes, and future directions. Task-based studies were considered consistent with the model if they reported subcortical hyperactivation and/or hypoactivation/hyperactivation of regulatory regions during emotion processing/regulation. Regarding positive stimuli, task-based studies were considered consistent with the model if they reported striatal hyperactivation in substance use and striatal hypoactivation in depression. Regarding resting state, lower-cortico-subcortical connectivity was considered consistent with the model. Decreased rsFC would correspond to decreased functional integration between cortical and subcortical structures and therefore reflect dysfunction in the emotion regulation circuitry. Due to a dearth of studies, especially for substance use, the variation in methods and analysis techniques used, and a general lack of concurrence between studies, for both depression and substance use/SUD, it was challenging to identify their common and distinct neural correlates. Although findings were largely inconsistent, a few patterns emerged.

5.1. Affective reactivity/affective modulation

Aberrant activation of emotion generating regions during affect processing has been implicated in depressed adults in several studies (Mayberg, 1997; Stuhrmann et al., 2011). Specifically, the amygdala has been shown to be hyperactive in adults with MDD in tasks of affective modulation, primarily in response to negative stimuli (Drevets, 2001; Rive et al., 2013; Sheline et al., 2001). In contrast, studies on adults with substance use disorders have had contradictory findings, with some

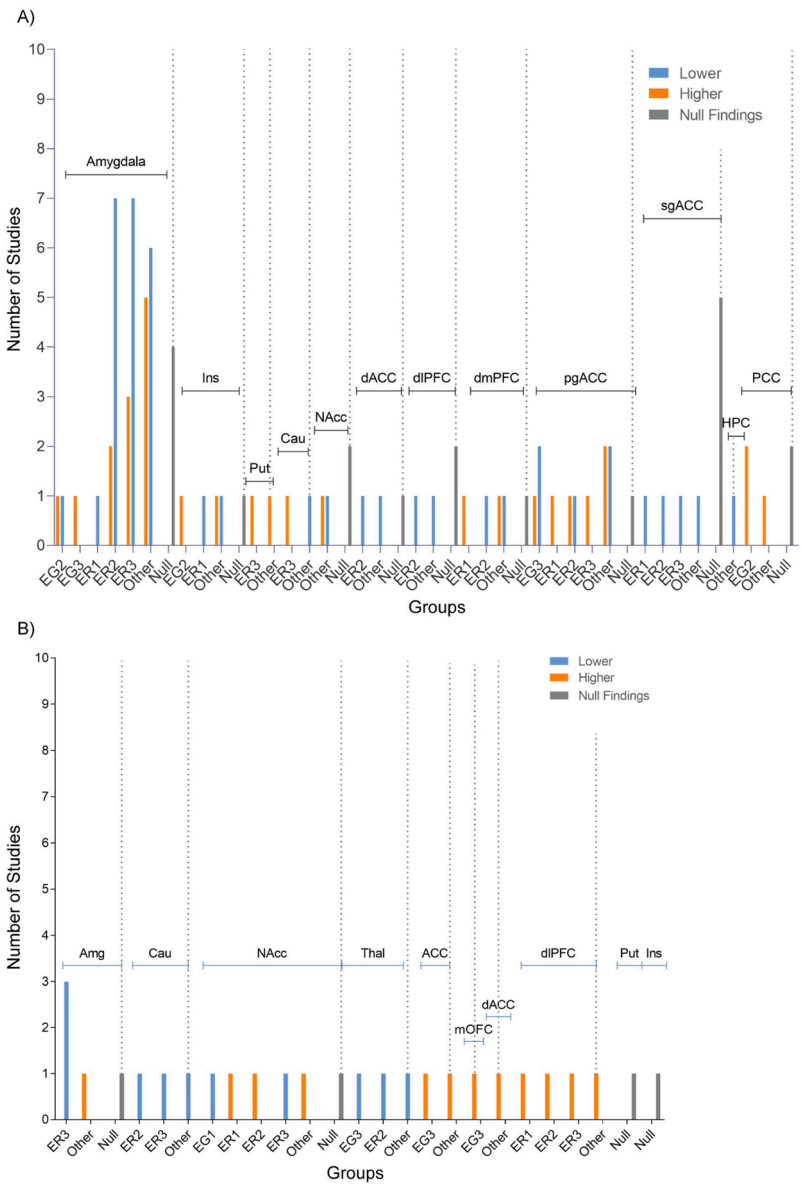

Fig. 3. Aberrant resting state functional connectivity. Histograms illustrating the number of studies that showed depression (A) and substance use (B) associated aberrant resting state functional connectivity between seed regions and EG1 (amygdala), EG2 (insula), EG3 (basal ganglia), ER1 (dmPFC/dACC/SMA/Pre-SMA), ER2 (dlPFC/vlPFC/lOFC), ER3 (rACC/vmPFC/mOFC/hippocampus) and other regions. Orange bars represent higher connectivity and blue bars represent lower connectivity. Gray bars represent null findings for each seed region. (For interpretation of the references to colour in the Figure, the reader is referred to the web version of this article).

studies finding no group differences in amygdala activation in substance-users and non-users, and other studies reporting hypo-activation or hyperactivation of the amygdala during tasks of affective reactivity and modulation (e.g., Jansen et al., 2019; Wang et al., 2010; for review see Wilcox et al., 2016).

Approximately half (n = 15/26) of the reviewed studies that investigated amygdala activity (whole-brain or ROI) in depressed youth found altered activity in this region. There was some consistency in the direction of findings; eight studies found heightened amygdala activation to negative stimuli. Although two studies found lower amygdala activation in response to negative stimuli (Beesdo et al., 2009; Thomas et al., 2001), it is possible that these findings could in part be explained by study samples and methodology. For example, one study (Thomas et al., 2001) that found decreased amygdala activity to negative stimuli in depressed adolescents had a sample size of only five MDD subjects. The two studies in substance using youth that reported amygdala activation abnormalities for negative stimuli had contradictory findings; increased amygdala activation in substance using adolescents (Spechler et al., 2015) and decreased amygdala activation in substance using emerging adults (Heitzeg et al., 2015) to negative faces. The difference in age between the two samples could be a possible explanation for this discrepancy. Of note, altered amygdala activation in response to positive stimuli was rarely reported in depressed and substance using youth.

It is important to note that of the depression studies that reported significant amygdala effects (n = 15), most (n = 13) used a ROI approach in their analysis, which entails less stringent correction methods than whole brain analyses. Of the 21 studies of youth depression that utilized affective reactivity/modulation paradigms and conducted whole-brain analyses, only two (~10%) reported aberrant amygdala activation during emotion processing (Henderson et al., 2014; Quevedo et al., 2018). Similarly, the three studies that found altered amygdala activation in response to emotional (positive; Gruber et al. (2009) or negative; Spechler et al. (2015); Heitzeg et al. (2015)) stimuli in substance use also used an ROI based approach. Interestingly, a meta-analysis of fMRI studies in youth depression did not find altered amygdala reactivity during affective processing (Miller et al., 2015). The fact that whole brain analyses often did not reveal altered amygdala activity raises questions about the robustness of significant amygdala findings; however, it is also suggested that the current methods of correction in whole-brain analyses may be too stringent to accurately determine small group differences in neural activation (Lieberman and Cunningham, 2009; Poldrack et al., 2017), which indicates that

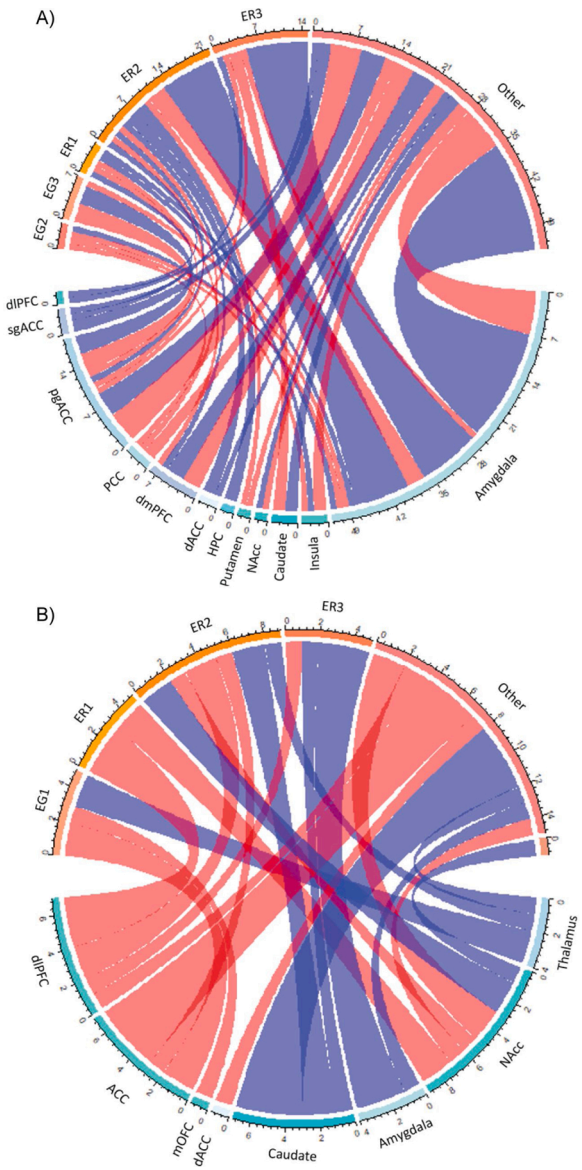

Fig. 4. Aberrant resting state functional connectivity. Chord diagrams depicting the number of instances reported for depression (A) and substance use (B) associated aberrant resting state functional connectivity between seed regions and EG1 (amygdala), EG2 (insula), EG3 (basal ganglia), ER1 (dmPFC/dACC/SMA/Pre-SMA), ER2 (dlPFC/vlPFC/lOFC), ER3 (rACC/vmPFC/mOFC/hippocampus) and other regions in A) depression and B substance use (multiple findings of increased or reduced seed-group rsFC within the same study were counted as separate instances). Regions in blue depict seed regions and regions in orange represent target groups. Blue chords represent decreased connectivity; red chords represented increased connectivity. (For interpretation of the references to colour in the Figure, the reader is referred to the web version of this article).

Brain regions: ACC = anterior cingulate cortex, dACC = dorsal ACC, dlPFC = dorsolateral prefrontal cortex, dmPFC = dorsomedial PFC, HPC = hippocampus, mOFC = medial orbitofrontal cortex, NAcc = nucleus accumbens, PCC = posterior cingulate cortex, pgACC = perigenual ACC, sgACC = subgenual ACC.

case-control differences in amygdala activation are likely minor.

Regarding the recruitment of prefrontal regions, in a review of emotion processing and regulation tasks in depressed adults, Rive et al. (2013) concluded that there is increased recruitment of prefrontal regions during automatic emotion regulation (i.e. affective reactivity/modulation). In contrast, a review by Wilcox et al. (2016) on studies of adults with substance use disorders concluded that there is dampened activity of regulatory structures while processing negative affect. Our review of the published literature found that although more studies reported increased activation of prefrontal regulatory structures relative to decreased in depressed youth, the direction of activation for prefrontal structures was divergent across contrasts, with no conspicuous pattern. Importantly, in contrast to amygdala activation, most studies that found altered prefrontal activation (n = 15 across contrasts) did so with whole-brain analyses. In the reviewed studies on substance using youth, decreased activation in response to negative stimuli (Heitzeg et al., 2015; Spechler et al., 2015), and increased activation in response to positive stimuli (Heitzeg et al., 2015; Schuckit et al., 2016) of ER2 (lPFC) regions was reported by two studies (n = 2/5).

Of note, the reviewed literature indicates that alterations in activation primarily exists in the ER2 (lPFC) and ER3 (rACC/vmPFC) groups in response to positive and negative stimuli in both depression and substance use. This is somewhat consistent with other literature. For example, a recent meta-analysis on youth depression reported dlPFC (i.e., ER2) hyperactivation in response to negative stimuli (Miller et al., 2015). Interestingly, our review of the literature demonstrated very little evidence for aberrant activation of ER1 (dmPFC/dACC) regions in depression and substance use. ER1 regions have been shown to be involved in the deciphering of emotional salience of stimuli during cognitive control (Duval et al., 2015; Phillips et al., 2008; Uddin, 2015), whereas ER2 (lPFC) and ER3 (rACC/vmPFC) are an integral part of the emotion regulation circuitry; ER2 regions (lPFC) are involved in voluntary emotion regulation whereas ER3 (rACC/vmPFC) regions are responsible for automatic emotion regulation. (Duval et al., 2015; Phillips et al., 2008; Uddin, 2015; Viviani, 2014). We thus postulate that depressed and substance using youth are not impaired in assigning value and importance to, but rather in the regulation of their response to emotional cues. A similar pattern was observed with respect to rsFC (discussed in subsequent sections) wherein amygdala to ER2 (lPFC) and ER3 (rACC/vmPFC), but not ER1 (dmPFC) regions was more often implicated in depression and substance use. This may imply that depressed and substance using youth share an underlying neurobiology associated with impaired emotion regulation such that they are able to attend to incoming emotional information and understand its salience, but their processing of it is impaired at two levels, both automatic and voluntary.

In addition, the reviewed literature shows aberrant activation of several "other" regions, such as the postcentral and precentral gyri, fusiform gyrus, thalamus and the superior temporal gyrus (STG). Notably, whole-brain analyses demonstrated the aberrant involvement of the fusiform gyrus in several studies of affective modulation in youth depression, with two studies finding higher activation for negative emotion processing (Henderson et al., 2014; Henje Blom et al., 2015), one study finding increased (Quevedo et al., 2018) and another decreased activation (Henje Blom et al., 2015) for positive emotion processing, and one study reporting increased activation to faces in general (Jenkins et al., 2016). In addition to coding face shape and identity, studies have shown that the fusiform areas are also sensitive to the emotional valence of faces (for review see Vuilleumier and Pourtois, 2007). This is consistent with the idea that depressed youth are impaired in emotion face processing, which could potentially contribute to the negative bias often reported in depression (Bourke et al., 2010; Elliott et al., 2011). Such an observation was not made for substance using youth in this review, which could in part be due to the small number of studies.

Although more work is required on substance use before unequivocal inferences can be drawn, we tentatively conclude that the current literature on affective reactivity and modulation paradigms support the idea that there is aberrant activity in the cortico-subcortical circuitry in both depression and substance use; however, findings regarding direction of activity and reactivity to positive versus negative stimuli are largely inconsistent. The most consistent finding was heightened amygdala reactivity to negative affective stimuli in depression.

Table 7
Affective reactivity and modulation paradigms in youth substance use.

Study	Methodological aspects						Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Task	Statistical Threshold and analysis method	ROI for activation analysis	Contrast	Regions	Recruitment/ connectivity in SU vs HC
Cyders et al. (2014)	Social drinkers = 38 (13 F)	25.19	21-35	Passive odor response	ROI CT FDR $p < 0.05$ CDT $p < 0.001$	mPFC	Craving inducing cues	Negative urgency traits were predictive of increased activation in the bilateral vmPFC in response to alcoholic odors vs sham odor and of subjective craving for alcohol.	
Gruber et al. (2009)	Heavy cannabis smokers = 15 (1 F)	25	NR	Masked facial affect paradigm (gender discrimination at the end of the image presentation)	WB and ROI WB: CT $p < 0.05$ $k >= 20$ CDT $p < 0.005$ ROI: CT $p < 0.05$ $k >= 20$	AMG, Cingulate gyrus	Masked angry faces	Midanterior cingulate	Lower
								Post cingulate*	Higher
								AMG	Lower
							Masked happy faces	Mid cingulate	Higher
								Post cingulate	Higher
								Amygdala	Lower
								L limbic lobe, cingulate gyrus	Lower
								Precuneus, R parietal lobe	Lower
								L parietal lobe, SPL	Lower
								R posterior lobe, cerebellar tonsil	Higher
							Masked angry faces	R temporal lobe, MTG	Higher
								R frontal lobe, IFG	Higher
								L temporal lobe, sub-gyral	Higher
								R parietal lobe, precuneus	Higher
								R frontal lobe, paracentral lobule	Higher
								R frontal lobe, SFG	Higher
								L temporal lobe, STG	Lower
							Masked happy faces	L sublobar, extra-nuclear	Lower
								R posterior lobe, cerebellar tonsil	Higher
								caudal dlPFC	Lower
Heitzeg et al. (2015)	Heavy cannabis users: 20 (8 F)	19.84	17-22	Emotion arousal word task	WB and ROI WB: CT $p < 0.05$ k by AlphaSim CDT $p < 0.005$ ROI: CT $p < 0.05$	AMG	Negative > neutral	R MTG	Lower
								R cuneus/lingual	Lower
								R STG/insula	Lower
								AMG	Lower
							Positive > neutral	R IPL	Lower
								R dlPFC	Lower
								AMG	Lower
Nikolova et al. (2016)	Total sample = 759 (426 F), AUD = 86 (35 F)	Total sample = 19.65, AUD = 19.94	18-22	Emotion processing & feedback-based number guessing task	ROI CT $p < 0.05$	AMG (emotion task), VS (monetary reward task)		Greater mismatch between VS and amygdala reactivity predicted greater risk for problem drinking	
Schuckit et al. (2016)	Low level alcohol response (LR) = 57 (50.9%F), high level	Baseline/follow up, LR = 19.8/	18-25	Matching faces on emotion or gender	ROI CT $p < 0.05$ k by MC	Insular cortex, mPFC, AMG	Happy	R MFG**	Higher
								L Ant Insula**	Higher
								B middle Insula**	Higher

(*continued on next page*)

Table 7 (*continued*)

Study	Methodological aspects						Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Task	Statistical Threshold and analysis method	ROI for activation analysis	Contrast	Regions	Recruitment/ connectivity in SU vs HC
	alcohol response (HR) = 57 (54.4%F)	24.9, HR = 19.9/ 25.2					Angry	R MFG**	Higher
					ROIs defined for clusters that survived angry > neutral contrast CT $p < 0.01$ k by MC CDT $p < 0.005$	MTG, IFG, ACC, Cerebellum, R Lingual gyrus, AMG		B AMG	Higher
Spechler et al. (2015)	Cannabis experimenting adolescents = 70 (20 F)	14.76	NR	Emotion face processing task			Angry > neutral	R MTG	
								B IFG	Lower
								OFC	Higher
							Negative > neutral	R mOFC - L AMG, L dorsal striatum (PPI)	Higher
Zimmerman et al. (2018)	Cannabis dependent = 19 (2 F)	23.79	18-35	Cued emotional pictures	WB and ROI for PPI WB: CT FWE $p < 0.05$ PPI: CT FWE-SVC $p < 0.05$	WB	Resting state	Cannabis users showed increased rsFC between the right mOFC and the left dorsal striatum.	

Abbreviations: Ant = anterior, AUD = alcohol use disorder, B = bilateral, CT = cluster threshold, CDT = cluster determining threshold, FDR = false discovery rate, FWE = family-wise error, HC = healthy controls, k = cluster extent, L = left, MC = Monte Carlo simulations, NR = not reported, PPI = psychophysiological interaction, R = right, ROI = region of interest, SU = substance use, WB = whole brain
Brain regions: ACC = anterior cingulate cortex, AMG = amygdala, dlPFC = dorsolateral prefrontal cortex, dmPFC = dorsomedial PFC, IFG = inferior frontal gyrus, IPL = inferior parietal lobule, MFG = middle frontal gyrus, mOFC = medial OFC, mPFC = medial PFC, MTG = middle temporal gyrus, OFC = orbitofrontal cortex, PCC = posterior cingulate cortex, PHG = parahippocampal gyrus, PFC = prefrontal cortex, preCG = precentral gyrus, SFG = superior frontal gyrus, SMA = supplementary motor area, STG = superior temporal gyrus, vmPFC = ventromedial PFC.
* correlated with number of smokes per week.
** predictive of poor alcohol related outcomes in the future.

5.2. Behavioral control

Subcortical activity has been found to be altered during tasks of behavioral control in both depressed and substance using adults (Rive et al., 2013; Wilcox et al., 2016). Studies have demonstrated that depressed adults show exaggerated reactivity of subcortical structures and attenuated reactivity of prefrontal structures to emotional distractors during behavioral control paradigms (e.g., Hare et al., 2008). Altered (lower) amygdala activation during behavioral control paradigms has been found in substance dependent adults (e.g., Smoski et al., 2011).

Behavioral control studies in depressed and substance using youth had some similar and some opposing findings. Greening et al. (2013) reported attenuated amygdala response to positive stimuli in depressed youth while Aloi et al. (2018) reported increased amygdala reactivity in substance using youth. With respect to negative stimuli, studies reported heightened amygdala response to negative stimuli associated with both depression (de Bellis and Hooper, 2012; Greening et al., 2013), and substance use (Aloi et al., 2018). Previous literature indicates that heightened amygdala response to negative stimuli may characterize risk for a subpopulation of those that abuse substances to manage high levels of negative affect (Gilman and Hommer, 2008; Nikolova et al., 2016). Despite higher subcortical activity in both depression and substance use with respect to negative stimuli, implicated cortical regions were less consistent. Findings from reviewed studies suggest that depression may be associated with increased recruitment of prefrontal emotion regulatory regions (de Bellis and Hooper, 2012; Kaiser et al., 2015). It is possible that increased recruitment of prefrontal structures may reflect the need for additional resources to regulate strong bottom-up subcortical reactivity, and that the task of ignoring negative distractors is especially cognitively taxing in depression (Kaiser et al., 2015; Rive et al., 2013). On the other hand, substance use studies (although fewer) showed a pattern of reduced prefrontal recruitment in substance users (Aloi et al., 2018; Cohen-Gilbert et al., 2017), which could be indicative of an inability to adequately recruit emotion regulatory structures to regulate subcortical hyperresponsiveness in the face of negative emotional distractors (Cohen-Gilbert et al., 2017).

Given the small number of studies, any conclusions drawn will be speculative; however, we can tentatively infer that both depression and substance use are associated with altered neural activity during regulation of engagement with emotional distractors. The direction of activation however, differs.

5.3. Cognitive modulation

Cognitive modulation paradigms involve voluntary regulation of one's affective state (Smoski et al., 2015; Wilcox et al., 2016). Studies have shown altered patterns of neural activity during cognitive reappraisal in depressed and substance using adults (Albein-Urios et al., 2014; Smoski et al., 2015). A recent meta-analysis of cognitive reappraisal studies showed heightened activation of several regions, including the insula, and attenuated activation of prefrontal regions (vlPFC, dmPFC) in depressed adults (Picó-Pérez et al., 2017). With respect to substance use, to our knowledge, there have been only two published studies of cognitive modulation in adults (Albein-Urios et al., 2014; Jansen et al., 2019). Albein-Urios et al. (2014) reported hypoactivation of emotion generating/processing regions, and top-down regulatory structures, whereas a recent study reported no group differences in neural activation associated with the cognitive reappraisal of negative affect in substance dependent adults (Jansen et al., 2019).

In youth depression, our review identified studies that have reported both amygdala hypo- and hyperactivation during cognitive reappraisal (Greening et al., 2014; Perlman et al., 2012; Stephanou et al., 2017). Hyperactivation of prefrontal structures in depressed youth was also reported in two studies (Perlman et al., 2012; Stephanou et al., 2017); however, for one of these studies, results did not survive correction for

Table 8
Behavioral control paradigms in youth substance use.

Study	Methodological aspects						Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Task	Statistical Threshold and analysis method	ROI for activation analysis	Contrast	Regions	Recruitment/ connectivity in SU vs HC
Aloi et al. (2018)	AUD = 21 (9 F), CUD = 29 (7 F)	AUD = 16.5, CUD = 16.2	14-18	Affective Stroop task	WB and ROI WB: CT FWE k by 3dClustSim $p < 0.001$ ROI: CDT $p < 0.02$	AMG	Positive > negative	AMG*	Higher
							Positive > neutral	AMG	Higher
								B dlPFC**	Lower
								B precuneus/ PCC	Lower
							Incongruent > congruent	R MFG	Lower
								R PCC	Lower
								R IPL	Lower
								R IPL	Lower
								R MTG	Lower
								L PHG	Lower
								R PCC***	Higher
								B Precuneus	Higher
							Incongruent > congruent	R IPL	Higher
								R MTG	Higher
								L Cerebellum	Higher
								L Culmen	Higher
Cohen-Gilbert et al. (2017)	Binge drinkers = 23(16 F)	18.8	18-20	Affective Go/ No-go	ROI CT FWE $p < 0.05$ CDT $Z > 2.3$	PFC, NAcc, AMG	Negative > neutral	dlPFC****	Lower
								dmPFC	Lower
								ACC	Lower

Abbreviations: AUD = alcohol use disorder, AUDIT = Alcohol Use Disorders Identification Test, B = bilateral, CT = cluster threshold, CDT = cluster determining threshold, CUD = cannabis use disorder, CUDIT = Cannabis Use Disorders Identification Test, FWE = family-wise error, HC = healthy controls, L = left, PPI = psychophysiological interaction, R = right, ROI = region of interest, SU = substance use, WB = whole brain
Brain region: sACC = anterior cingulate cortex, AMG = amygdala, dlPFC = dorsolateral prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, IPL = inferior parietal lobule, MFG = middle frontal gyrus, MTG = middle temporal gyrus, PCC = posterior cingulate cortex, PHG = parahippocampal gyrus, preCG = precentral gyrus, SFG = superior frontal gyrus, SMA = supplementary motor area

* correlated with audit scores.
** negatively correlated with audit scores.
*** correlated with CUDIT scores.
**** negatively correlated with last three-month binges.

Table 9
Cognitive modulation paradigms in youth substance use.

Study	Methodological aspects No. of subjects (females)	Mean Age	Age-range	Task	Statistical Threshold and analysis method	ROI for activation analysis	Significant findings Contrast	Regions	Recruitment/connectivity in SU vs HC
Zimmerman et al. (2017)	Cannabis users = 23 (0 F)	21.24	18-40	Cognitive reappraisal task	WB, ROI and ROI for PPI CT FWE p < 0.05 CDT T = 3.09	AMG	Reappraise > maintain	B preCG	Higher
								R SFG	Higher
								L mid-cingulate/ SMA	Higher
								AMG	Higher
								L AMG - L dlPFC (PPI)	Lower

Abbreviations: B = bilateral, CT = cluster threshold, CDT = cluster determining threshold, FWE = family-wise error, HC = healthy controls, L = left, PPI = psychophysiological interaction, R = right, ROI = region of interest, SU = substance use, WB = whole brain
Brain regions: AMG = amygdala, dlPFC = dorsolateral prefrontal cortex, preCG = precentral gyrus, SFG = superior frontal gyrus, SMA = supplementary motor area

multiple comparisons (Stephanou et al., 2017). Studies have also reported no group differences in activation during the reappraisal of negative affect (Platt et al., 2015; LeWinn et al., 2018). In substance using youth, the only published study, to our knowledge, using a cognitive reappraisal paradigm, found higher activation of emotion generating (amygdala) and emotion regulating regions (dlPFC and SMA) during cognitive reappraisal. PPI results for depression and substance use and were opposing; increased cortico-subcortical connectivity in depression (Perlman et al., 2012; Platt et al., 2015) and lower connectivity in substance using youth (Zimmerman et al., 2017).

In summary, the neural correlates of cognitive reappraisal have not been adequately explored in youth depression and substance use. Moreover, existing research is generally inconsistent, making reconciling and interpreting results challenging.

5.4. Aberrant resting state functional connectivity

Studying functional connectivity during rest allows researchers to study stable neural connections, independent of a task, that may be linked to complex behavior and psychopathology (Fox and Greicius, 2010). Indeed, resting state fMRI possesses several advantages over task fMRI, especially for clinical populations. It allows the study of clinical populations independent of task-related confounds (Fox and Greicius, 2010). Decreased rsFC between prefrontal and subcortical regions has been posited to be a characteristic of dysregulated affect (Drevets, 2001), and has been consistently found both in adults with depression (Kaiser et al., 2015) and in adults with SUD (Gu et al., 2010; Upadhyay et al., 2010; Wilcox et al., 2016).

We identified several studies (n = 17/29) assessing rsFC in youth depression that used the amygdala as a seed region for their analysis. Most studies (n = 13/17) used a seed-to-voxel approach, and a few created masks based on *a priori* hypotheses (Bebko et al., 2015; Davey et al., 2015; Geng et al., 2016; Jalbrzikowski et al., 2017). The majority of these studies found reduced amygdala-PFC connectivity in depression, specifically with ER2 (lPFC) and ER3 (rACC/vmPFC) regions. Far fewer studies exist on youth substance use, with our search yielding only four studies that have used the amygdala as a seed region in rsFC analysis (Crane et al., 2018; Peters et al., 2015, 2017; Weissman et al., 2015). Three out these four studies found reduced amygdala-ER3 (mOFC) connectivity, with connectivity between these specific regions also observed by two studies in depressed youth (Fischer et al., 2018; Zhang et al., 2014).

It is important to note that although most studies in youth depression did find lower connectivity between the amygdala and regulatory regions, a few found increased amygdala connectivity in depressed youth (Burghy et al., 2012; Davey et al., 2015; Pannekoek et al., 2015), and two found unaltered amygdala connectivity (Cullen et al., 2009; Hirshfeld-Becker et al., 2019); however, Davey et al. (2015) used a seed-to-mask approach for the sgACC, which requires less stringent correction, and Becker et al. (2019) and Cullen et al. (2009) had small sample sizes (n = 10 and 12, respectively), which makes it more difficult to reject a null finding (Button et al., 2013). In addition, unlike most other studies that had lower numbers, more than 90% of depressed participants in Cullen et al. (2009) and Pannekoek et al. (2015) had comorbidities, which likely introduces variability (Rive et al., 2013).

In summary, consistent with adult studies, most studies on depressed and substance using youth found lower connectivity between the amygdala and prefrontal regulatory regions. Specifically, reduced connectivity between the amygdala and ER2 (lPFC) and ER3 (rACC/vmPFC) groups was apparent in depressed youth, and connectivity between the amygdala and ER3 regions was reduced in substance using youth compared to controls. Consistent with task-based studies, ER1 regions (dmPFC) were rarely implicated. Thus, findings may indicate that intrinsic functional connectivity in depressed and substance using individuals underlies difficulties in regulating emotional responses, rather than impairment in assessing the salience of emotional cues.

Table 10
Aberrant resting state functional connectivity in youth substance use.

Study	Methodological aspects					Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Statistical Threshold and analysis method	Seeds for connectivity analysis	Seed	Target	Connectivity in SU vs HC
Camchong et al. (2014)	T1 (imaging): SUD = 18 (8 F) (5 weeks abstinent), T2 (imaging): 12 SUD (5 F) (13 weeks abstinent), T3 follow up at 6 months to record relapse (12 abstainers, 6 Relapsers)	22.05	18-25	Seed to voxel CT FWE $p < 0.025$ k by MC CDT $p < 0.005$	NAcc, sgACC		No group differences in rsFC reported at T1 between SUD and HC	
						NAcc	PCC	Higher (Relapsers > HC)
						sgACC	FPC	
						NAcc	FPC	Greater reduction from T1 to T2 (Relapsers > HC)
						NAcc	PCC	
						sgACC	FPC	
Crane et al. (2018)	Binge drinkers = 39 (10 F)	25.9	21-34	Seed to voxel and PFC mask Mask: CT FWE $p < 0.05$ WB: CT $p < 0.05$ k by MC CDT $p < 0.001$	AMG	R AMG	OFC	Lower
Huang et al. (2014)	Smokers = 11 (?F)	23.7	18-39	Seed to voxel CT $p < 0.05$CDT $p < 0.001$	DMN, ACC	R AMG	ACC Caudate Putamen	Higher (abstinent smokers > nonsmokers)
						DMN	Middle frontal area preCG MFG	
(Lee and Telzer, 2016)	Total sample = 37 (18 F)	14.7	13-17	group ICA	Limbic network and R FPN		More negative coupling between the Limbic network and R FPN was predictive of later age of onset of substance use and higher self-control. The group that never used substances showed greater anticorrelation between the two networks.	
Manza et al. (2018)	Cannabis abuse = 30 (8 F) (HCP data)	29.17	18-34	Seed to voxel and basal ganglia nuclei CDT $p < 0.005$	Dorsal midbrain, lateral thalamus, ventral striatum, brain stem		No group differences in rsFC reported	
Peters et al. (2015)	Comm sample = 173 (86 F)	15.85	12.05-25.95	Seed to voxel and OFC mask CT $p < 0.05$ CDT $Z > 2.3$	AMG	AMG	Testosterone influenced alcohol use through amygdala-OFC connectivity, for recent (bilateral AMG-OFC connectivity) and lifetime ((right AMG-OFC connectivity) alcohol use for boys. No mediation effects were found in girls.	
Peters et al. (2017)	Sample at T1 = 193, T2 = 244	T1 = 14.06, T2 = 15.90	T1 = 8-25, T2 = 10-27 (alcohol consumption data only available for 12 and up)	Seed to voxel and OFC mask CT $p < 0.05$ CDT $Z > 2.3$	AMG	AMG	Significant effect of AMG-OFC connectivity at T1 on alcohol consumption two years later; less positive connectivity at T1 was associated with increased alcohol consumption at T2.	
Posner et al. (2016)	SUD = 15 (5 F)	25.6	25-27	Seed to OFC, amygdala, hippocampus, NAcc, and midbrain/VTA CT FWE-SVC $p < 0.05$	NAcc	L NAcc	L OFC	Lower
							L AMG	Lower
							L PHG	Lower
						R NAcc	B PHG	Lower
Subramaniam et al. (2018)	MJ using = 43 (3 F)	18	14-20	Seed to voxel Within group CT FDR $p < 0.05$ k > 100 Between group: CDT $p < 0.005$, k > 20	OFC	OFC	No group differences in OFC seeded rsFC between MJ using and HC reported	
Wang et al. (2017)	Smokers = 24 (0 F)	20.8	18-24	Seed to voxel CT FWE $p < 0.005$ k by MC CDT $p < 0.005$	Thalamus	L Thalamus	B Caudate	Lower
							R ACC	Lower
							R dlPFC	Lower
							B Insula	Lower

(*continued on next page*)

Table 10 (*continued*)

Study	Methodological aspects					Significant findings		
	No. of subjects (females)	Mean Age	Age-range	Statistical Threshold and analysis method	Seeds for connectivity analysis	Seed	Target	Connectivity in SU vs HC
Wei et al. (2016)	Smokers = 21 (1 F)	26.38	18-40	Seed to voxel CT FDR $p < 0.05$	Ant insula, dACC, thalamus	R Thalamus	R dlPFC	Lower
						dACC	Thalamus*	Higher
Weissman et al. (2015)	Total sample = 69 (40 F), 40 participants had tried any substance in the last 7 years	16.26	10-16	Seed to voxel CT $p < 0.01$ k by MC CDT $p < 0.001$	NAcc, AMG, dlPFC	R dlPFC	R mPFC**	Higher
						R dlPFC	vmPFC**	Higher
						R dlPFC	R dmPFC**	Higher
						R dlPFC	L dlPFC**	Higher
						R dlPFC	R Lingual gyrus**	Higher
						R dlPFC	L vlPFC**	Higher
						L dlPFC	R ACC**	Higher
						NAcc	R preSMA/dlPFC**	Higher
						NAcc	R IPL**	Higher
						NAcc	R dmPFC**	Higher
						NAcc	R dlPFC**	Higher
						NAcc	R MTG**	Higher
Yuan et al. (2016)	Smokers = 60 (7 F)	20	16-24	Seed to voxel CT FWE $p < 0.0083$ (0.05/6)	Caudate, putamen, and NAcc	L Caudate	B ACC	Lower
							B Thalamus	Lower
							R MFG	Lower
							B ACC	Lower
							B IFG	Lower
						R Caudate	B Thalamus	Lower
							B Angular Gyrus	Lower
							R MFG	Lower
							R HPC	Lower

Abbreviations: Ant = anterior, AUD = alcohol use disorder, B = bilateral, Comm = community, CT = cluster threshold, CDT = cluster determining threshold, FDR = false discovery rate, FWE = family-wise error, HC = healthy controls, k = cluster extent, L = left, MC = Monte Carlo simulations, MJ = marijuana, NR = not reported, PPI = psychophysiological interaction, R = right, ROI = region of interest, rsFC = resting state functional connectivity, SU = substance use, SUD = substance use disorder, SVC = small volume correction, T = time, WB = whole brain.

Brain regions: ACC = anterior cingulate cortex, AMG = amygdala, dACC = dorsal ACC, dlPFC = dorsolateral prefrontal cortex, DMN = default mode network, dmPFC = dorsomedial PFC, FPC = frontopolar cortex, FPN = frontoparietal network, HPC = hippocampus, ICA = independent component analysis, IFG = inferior frontal gyrus, IPL = inferior parietal lobule, MFG = middle frontal gyrus, mOFC = medial OFC, mPFC = medial PFC, MTG = middle temporal gyrus, NAcc = nucleus accumbens, OFC = orbitofrontal cortex, PCC = posterior cingulate cortex, PFC = prefrontal cortex, PHG = parahippocampal gyrus, preCG = precentral gyrus, sgACC = subgenual ACC, SFG = superior frontal gyrus, SMA = supplementary motor area, STG = superior temporal gyrus, vmPFC = ventromedial PFC, vlPFC = ventrolateral PFC, VTA = ventral tegmental area.

* correlated with Fagerstrom Test for Nicotine Dependence (FTND) score.

** correlation with years since age 10 of substance use.

Interestingly, altered connectivity of ER1 regions (dmPFC/dACC/SMA/Pre-SMA) with other regulatory structures (e.g., sgACC, dmPFC, pgACC) was reported relatively more often (Pannekoek et al., 2015; Rzepa and McCabe, 2018; Strikwerda-Brown et al., 2015) than connectivity of ER1 regions with emotion generating regions in depression, indicating the likely importance of connectivity in other networks for depression (elaborated upon in section 5.6). The dmPFC/dACC (ER1) acts as a hub, such that it interacts with the PCC/precuneus (part of the default mode network (DMN)) which are responsible for self-referential processing, and cortical regions involved in cognitive control (Kaiser et al., 2015; Wilcox et al., 2016). It has thus been suggested that it plays a role in resource allocation between internal and external attentional systems (Menon and Uddin, 2010; Sridharan, 1980). This resource allocation is likely dynamic and adapts based on situational demands (Corbetta et al., 2008). Thus, lower connectivity of ER1 (dmPFC) regions with other cognitive control regions could indicate a disproportional allocation of attention to internal processes and thought, which may play a contributory role in the development or manifestation of depression.

5.5. Longitudinal imaging studies

Longitudinal work is undoubtedly important for identifying potential biomarkers and prodromal phases of disorders, for understanding typical and atypical developmental trajectories, and importantly for providing support for dual systems models; however, very few studies utilizing longitudinal imaging were identified in this review. Our search identified some longitudinal rsFC studies on youth depression (Davey et al., 2015; Jalbrzikowski et al., 2017; Strikwerda-Brown et al., 2015). Methods in the three studies were too divergent to identify commonalities; however, the amygdala and subgenual cingulate were frequently implicated. Additional longitudinal imaging work is required to study developmental trajectories and their association with behavioral and mental health outcomes.

5.6. The dual systems model and future directions

The dual-systems model suggests that youth are predisposed to affect dysregulation and risky behavior such as substance use due to the developmental mismatch between the rapidly developing subcortical system during adolescence, and the more slowly developing prefrontal system of top-down control (Casey and Jones, 2010; Casey et al., 2011; Gladwin et al., 2011; Steinberg, 2010a). The developmental mismatch model has been influential because of substantial evidence showing that the two systems undergo significant structural changes (Casey et al., 2008; Steinberg, 2008; Casey, 2015), and function differently during adolescence; however, there has been little empirical work directly exploring correlations of the developmental mismatch with psychopathological outcomes and behavior (Pfeifer and Allen, 2012).

We reviewed the existing literature to establish if depression and substance use are associated with altered cortical and subcortical activity, and aberrant cortico-subcortical connectivity in ways that are consistent with the dual-systems model. The reviewed literature showed that for most affective tasks, implicated regions and direction of reported alterations were largely inconsistent across studies, and

activation of "other" regions was also often reported to be aberrant (as discussed in section 5.1). However, findings were supportive of the model primarily in two ways: 1) amygdala hyperactivation in response to negative and neutral stimuli was consistently found for youth depression, and 2) lower cortico-amygdalar connectivity during rest was apparent in youth depression and substance use. In addition, both hypoactivation and hyperactivation of top-down regulatory structures was reported in several studies of emotion processing and regulation. While altered activity in regulatory structures was proposed to be consistent with the model, the lack of consistency in the direction of alterations does not allow for clear interpretation of findings.

Taken together, we suggest the following (not necessarily mutually exclusive) possibilities regarding support for the model. First, the model may be valid if we consider rsFC findings as most reliable. There is some evidence for superior reliability of rsFC as compared to task-based activation measures (Choe et al., 2015; Herting et al., 2018; Plichta et al., 2012). Further, methodological differences may explain findings of both increased and decreased cortical activation in depression/substance use during emotion processing/regulation (as discussed in section 5.7). Studies often interpret both findings as indicating impaired emotion regulation. For instance, hypoactivation of regulatory structures has been interpreted to reflect an inability to recruit cortical regions for top-down control (Colich et al., 2016), while hyperactivation has been suggested to reflect compensatory recruitment to overcome decreased cortico-subcortical coupling (Rive et al., 2013). To more accurately interpret findings of task-dependent activation, studies should examine associations between activation patterns and behavioral measures of emotion regulation obtained through self-report and/or behavioral paradigms. For example, studies might correlate patterns of neural activation during emotion regulation with self-reported measures of trait emotion regulation strategies (e.g., Grecucci et al., 2013). However, it is important to note that larger sample sizes may be required to establish reliable brain-behavior relationships (Masouleh et al., 2019). In addition, connectivity analyses more directly examine relationships between prefrontal and subcortical structures. As such, task-based activation studies should also conduct functional connectivity analyses (e.g., PPI and/or rsFC), which would aid in determining whether lower functional integration of cortical and subcortical regions more consistently corresponds to increased or decreased activation of top-down regulatory regions, thus allowing for clearer interpretation of findings in terms of the dual systems model.

Second, given that relatively more depression studies reported lower amygdala-ER2/ER3 (lPFC/rACC/vmPFC) rsFC and amygdala hyperactivity in response to negative affect, it is possible that the model is more applicable to depression than to substance use. As alluded to above, and discussed further in section 5.7.3, there may be more heterogeneity in the nature of emotion regulation deficits in substance using adolescents (e.g., poor regulation of negative versus positive affect) and neural underpinnings may differ accordingly. Third, the model may be incomplete or too simplistic. This point is elaborated on further below.

Other neurobiological models have also attempted to explain adolescence-associated behavioral changes and peak in hazard rates of depression and substance use. Ernst et al. (2006) proposed a "triadic" model whereby the maturation of "approach" system (ventral striatum) occurs before the "avoidance" system (amygdala) in adolescence, and that the still immature "regulatory" system (medial/ventral PFC) – the third arm of the triad – is unable to correct for this mismatch. This model also implicates the relationships between cortical and subcortical structures (the arms of the triad) in the youth-associated increase in depression. In line with this model, our review of youth depression literature showed decreased rsFC in the arms of the triad; specifically, several studies showed lower rsFC between the amygdala and lPFC (ER2) and ER3 (rACC/vmPFC) regions, and one study showed increased connectivity between the striatum and ER3 regions. There are other models of depression that focus on the neurobiology of reward processing (Davey et al., 2008; Forbes and Dahl, 2005), and which the current review is not able to evaluate given that we did not focus on studies of reward, specifically. Future work is needed to evaluate the validity of these models in light of current empirical literature. Finally, in order to verify (or falsify) the applicability of the dual systems model in depressed and substance using youth, future work should include both adolescents with depression (but without substance use issues), adolescents with problematic substance use (but without depression), and adolescents with comorbid depression and substance use issues in one longitudinal design. This would allow for the direct comparison of these cohorts in the same design, and provide insight into the common and distinct neural correlates of depression and substance use from a developmental perspective, as well as advance our understanding of depression-substance use comorbidity.

In any case, while the dual systems model provides a basic neurodevelopmental framework to explain adolescent-associated dysregulated affect and behavior, it is perhaps over simplistic (Casey, 2015). More longitudinal work is required for us to understand the finer nuances of changes in architecture of the brain with age and psychopathology. For instance, a recent longitudinal study by Duijvenvoorde et al. (2019) showed that age related changes in connectivity between the PFC and subcortex were region specific; with some pairs showing increased connectivity, and some showing decreased connectivity with age in a large sample of typically developing adolescents (Duijvenvoorde et al., 2019). The implication of this on atypical development is yet to be explored. While there is some evidence of depression-associated changes in seed-based connectivity over time (e.g., Davey et al., 2015), much remains to be explored, and continued use of these models may act as a barrier to the conceptualization of new developmental frameworks (Casey, 2015). Generally, there is a need for increased specificity of developmental models (Pfeifer and Allen, 2016). Along with longitudinal work, the need for more rigorous statistical approaches to test these hypotheses has also recently been highlighted in the literature (Meisel et al., 2019).

It has been suggested that the functional and anatomical connections between different regions, rather than the regions themselves may underlie vulnerabilities (Whittle et al., 2006). Given that results from the reviewed literature are largely not concurrent, and various brain regions have been implicated, the authors postulate that developmental impairments associated with mental illness are likely not region specific; but rather result from atypical neural interactions in the human connectome. Looking at the brain from a network/whole-brain perspective, instead of isolated regions or connections is likely to be more informative for multiple reasons; first, we know that changes in synaptic connectivity and myelination are key developmental processes at the micro-scale (Collin and Van Den Heuvel, 2013). Volumetric changes in grey and white matter have been consistently shown across adolescence and emerging adulthood (Giedd and Rapoport, 2010), and it has been suggested that such changes likely correspond with developmental changes in functional and anatomical connectivity at both micro and macro sales (Vértes and Bullmore, 2015). Second, higher order cognitive functions are not localized to specialized regions but rather arise from large-scale network interactions of both proximal and distal cells populations (Dehaene et al., 1998). Behavioral changes that accompany adolescence, and the increase in rates of mental illness during youth, could therefore be associated with changes in network-based interactions. Looking at wiring of the brain in entirety, with methods such as graph theory, will likely give us insight into developmental miswiring and its association with psychopathology (DiMartino et al., 2014). Recent work using network-based approaches has revealed age, and illness associated changes in the brain's network architecture (DiMartino et al., 2014; Uddin, 2010). For example, research has already shown that brains of depressed individuals have an aberrant topological organization (for review see Gong and He, 2015). More longitudinal work will be required to establish clear associations between network neuroscience and mental health.

5.7. Methodological issues

5.7.1. Sample size

Sample sizes of the reviewed studies are relatively modest, with a mean of 24, median 20 and range of 5–82 for MDD (excluding large cohorts with dimensional measures). Including studies of dimensional measures, the mean sample size was to 32.08 (range = 5–167, median = 24). For substance use, most studies utilized dimensional measures, with a mean sample size of 48.6 (range = 11–292, median = 27). Small sample sizes limit the interpretability of results, and lower the chances of replicating results (Thirion et al., 2007), which could explain why studies using the same paradigm have contradictory findings (Rive et al., 2013).

5.7.2. Task design

Task design was not consistent across studies, specifically with respect to stimulus type (pain, pictures, faces, words), the valence (positive, negative), varying intensity of the valence (100%/50% positive/negative), the stimuli (happy, sad, fearful, angry, neutral) and the contrasts examined during analysis (e.g., positive > negative vs positive > rest vs faces > shapes). This much diversity in the methods and analysis also introduces some inconsistency in the literature and likely results in divergent and contradictory findings (Müller et al., 2017). Attempting to limit synthesis of studies to those that used comparable paradigms and contrasts is currently not possible given the current relatively small literature base.

5.7.3. Treatment history and clinical characteristics

The lack of consistent findings across studies could also be attributed to the variance in treatment history, comorbidities and clinical characteristics of the participants. It is known that functional activity and connectivity in depressed as well as remitted MDD participants is altered by anti-depressant use (Delaveau et al., 2011; Kumar et al., 2008; Wang et al., 2008). It can thus be inferred that medication is likely a significant confounding factor. In our reviewed literature, of the studies that reported medication status, 20 out of the 65 studies that reported medication status included currently medicated depressed patients and 0/23 included medicated substance using youth. The effects of medication on the results are difficult to establish, because of the heterogeneous profile of treatment, and the small number of studies that directly studied the effect of medication on the neural correlates of emotion processing and regulation. In addition, a small number of studies in youth depression (n = 10) did not report medication status, and we would encourage future studies to include information about medication use to aid replication and comparisons between studies. Similarly, of the studies that reported comorbidities, more than 50% of MDD subjects had another Axis I disorder. Several studies on substance using youth included in our review also used participants with Axis I disorders including MDD (e.g., Aloi et al., 2018; Heitzeg et al., 2015). Thus, comorbidity is also likely an important confound (Rive et al., 2013). Depression severity could also potentially be an important confounder since neural activity and functional connectivity between regions have often been shown to be correlated with the severity of depression; however, only a few studies reported these associations (Bebko et al., 2015; Burghy et al., 2012; Fowler et al., 2017; Hall et al., 2014; Ho et al., 2015, 2014). Finally, depression itself is a complex clinical disorder, in that the primary symptom could be depressed mood and/or anhedonia, and other symptom profiles can be variable (Rive et al., 2013). Therefore, this diverse clinical presentation of the disorder may prevent us from being able to decipher the underlying pathophysiology of depression.

Similarly, underlying causes for substance use are also variable; for example, individuals may take to substances to reduce negative affect, increase experience of affect when emotions are absent, or control affect when emotions are confusing or excessive (Khantzian, 1997). The recruitment of larger and more homogenous cohorts will help decipher the underlying pathophysiology of depression and substance use. Alternatively, use of classification frameworks such as Research Domain Criteria (RDoC), (Insel et al., 2010) rather than case-control designs, would help us understand the neurobiology of different presentations of a disorder and help characterize its clinical diversity.

Regarding substance use, due to the small number of studies, the extant literature did not permit us to examine substance use disorder and substance use separately. We reviewed studies across substances and with differing clinical profiles, which included recreational use, problematic use and substance use disorders, which likely introduces variability (Chye et al., 2017; Vonmoos et al., 2013; Zhou et al., 2019). Differences in neural activity during emotion processing/regulation based on severity of use/dependence was not possible for us to discuss in this review given that limited research has been conducted. More studies exploring emotion regulation and processing are required in substance using youth before definitive conclusions can be drawn.

5.7.4. Data analysis and interpretation

Studies used different methods in their analysis with respect to the contrasts examined (emotion compared to fixation/rest or another valence), signal type (group differences in activation vs deactivation), statistical approach to the analysis (ROI vs whole-brain for task and seed-to-voxel vs seed to mask/ROI for connectivity), seeds and ROIs chosen for analyses, and finally statistical correction methods employed for multiple comparisons. For instance, ROI based approaches are less stringent in nature and therefore the rate of false discovery is higher, whereas Type II error rates are higher with whole-brain correction methods (Lieberman and Cunningham, 2009; Poldrack et al., 2017). Finally, due to the statistical thresholding methods used in past studies, there is an increased risk of inflated false positives in some of the earlier studies (Eklund et al., 2016). Therefore, data analysis can also introduce significant variability in results.

It is also worth mentioning that the reporting and interpretation of findings in resting functional connectivity studies can be quite variable. Frequently, group-specific values of functional connectivity findings are not reported, and results are limited to increased vs decreased connectivity between groups, which do not permit further discourse on positive vs negative connectivity, and the difference in connectivity strengths. Future studies should aim to provide more nuanced interpretations of weak (close to zero) vs strong (positive or negative) connectivity or positive vs negative connectivity between groups.

5.8. Limitations

This review has some limitations worth discussing. First, the literature on emotion processing/regulation and resting state connectivity in youth depression is far more comprehensive than that on substance using youth. As such, more studies in substance use are needed to further explore patterns in altered neural circuitry within each dimension (affect intensity/modulation, cognitive modulation and behavioral control) and resting state. Second, most studies in depression have majority female samples while most studies in substance use have majority male samples, which makes comparisons more difficult, especially given that studies have shown sex differences in the neural correlates of emotion regulation (e.g., Potenza et al., 2012). Third, due to the small number of studies, this review did not differentiate between recreational use and substance dependence, nor did it differentiate between different substances. This is an important topic for future research and reviews to address. Further, this review examined neural circuitry of emotion processing and regulation in active depression, subclinical depression, remitted depression and correlations with dimensional measures of depression and as such it is possible these different forms of depression may have distinct underlying neurobiology. There is some evidence however for similar neurobiological alterations in subclinical and clinical depression (Brakowski et al., 2017). In addition, in order to determine if including studies with current MDD versus subclinical or other types of depression had an impact on consistency, we conducted a

preliminary analysis of affective reactivity/modulation paradigms—the dimension with the most of number of studies— in current MDD only, and found little difference in the pattern of findings (Supplementary Fig. 2) to those reported in section 4.3.1.1. Fourth, given the lack of longitudinal studies (noted above) or studies assessing discrete age periods, we were unable to comment on developmental effects. As a supplementary analysis, we provide figures separately for adolescents and emerging adults (Supplementary Figure 3–5). However, studies were too few in number to observe differences between these age groups. Finally, our review included some studies with an upper age that was greater than 29 (n = 7 in depression and n = 7 in substance use) or unknown (n = 3 in depression and n = 1 in substance use). This decision was made due to the small number of substance use studies where all participants were within the age range 10–29 (n = 16 across three dimensions of emotion regulation, and resting state). However, it is important to note that excluding these studies from the review would not have altered our main conclusions regarding increased amygdala activation to negative stimuli in depression, and decreased connectivity between the amygdala and prefrontal regulatory structures in both youth depression and substance use.

6. Conclusion

This review aimed to evaluate the validity of the dual systems model for youth depression and substance use. We reviewed the extant literature on emotion processing and regulation tasks, and resting state functional connectivity, in order to examine alterations in the emotion processing/regulation circuitry. We found that while some patterns consistent with the dual systems model emerged, the literature was generally divergent. It is likely that network-based and other whole-brain approaches and more longitudinal work will help us better understand depression and substance use associated alterations in brain network architecture and developmental trajectories.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2020.100775.

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