Affect Regulation in Pediatric Bipolar Disorder

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INTRODUCTION

Bipolar disorder (BD) is among the most significant health problems for adults in America today, causing great morbidity, mortality, and over $40 billion in annual healthcare expenditures, we know far less about BD in children and adolescents [1]. Recent data indicate that pediatric BD (PBD) is a growing health problem whose incidence has risen 40-fold in the past decade, now accounting for 20% of all minors discharged from psychiatric hospitals [2;3]. It remains unknown if this increase represents greater awareness of a serious psychiatric disorder once thought not to exist in children or adolescents, or if it represents the diagnosis being too broadly applied. Determining which of these possibilities is correct is further complicated by the fact that there is no lab test for BD or any other psychiatric disorder, whether in children or adults. Instead, establishing the diagnosis of BD (or any other psychiatric disorder) is based entirely upon detailed clinical history that is often more difficult to elicit from minors than from adults. Thus, there is a pressing need to identify bio-behavioral markers of BD that could augment clinical history in the diagnostic and treatment process, especially for children and adolescents.

Towards that end, clinicians and researchers alike have been using the language of neuroscience to describe PBD patients as having "affect regulation problems." While our understanding of PBD has advanced thanks to such neurobiological research, some have suggested that thinking of BD youth as suffering from affect regulation problems may be an oversimplification, akin to stating that a febrile child is suffering from "temperature regulation problems"—i.e., factually true, but not illuminating the situation sufficiently to render a diagnosis and a treatment [4]. Clinicians and parents may wonder "does affect regulation improve what we know about the diagnosis and treatment of PBD, or does it further complicate matters?"

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In a word, our answer is "yes": while adding complexity and depth, we believe affect regulation does improve what we know about PBD. Affect regulation provides a framework for conducting biological research to identify the underlying mechanisms of BD, ultimately improving our care for these youth. While numerous books, manuscripts, and presentations have begun to address this topic, our present manuscript is intended to provide a concise and current guide to affect regulation in PBD, incorporating the latest in research as well as highlighting goals for the future. First, we will review the basics of affect regulation [5]. Then, we will discuss what is known about the three important affects in BD: irritability, euphoria, and depression. Finally, we review what is known about affect regulation in PBD.

AFFECT REGULATION BASICS

What is affect regulation? Clinicians and researchers alike often report BD youth as suffering from "affect regulation problems", including having abnormally high highs, low lows, and frequently shifting between the two, without maintaining much stability. Moreover, the pharmaceutical industry has seized upon this notion by using the term "mood stabilizer" to refer to medications used to treat BD, despite the fact that such medications are incredibly heterogeneous in terms of their pharmacological mechanisms [6;7].

Further complicating matters is the fact that the terms "emotion", "feeling", "mood", and "affect" are used interchangeably. Clinically, mental health professionals routinely distinguish between "mood" and "affect" when evaluating and treating patients, whether child or adult, in their formal mental status examination. In this context, the term "mood" usually refers to the patient's self-assessment of their emotional state (e.g., happy, sad, worried), whereas "affect" usually refers to the mental health professional's objective, observable assessment of the patient's emotional state and responsiveness (e.g., emotional state: depressed, euphoric, euthymic; emotional responsiveness: blunted, flat, expansive). The term "feeling" is often used similarly to "mood" as describing an individual's conscious awareness of their emotional state (e.g., I feel happy, sad, worried). Yet, there is no universal agreement among clinicians or researchers on the distinction between the terms "emotion" and "affect". Some use these terms interchangeably. In contrast, others suggest that "affect" is a biological, innate, instinctive response and "emotion" is the individual's memory of prior affects, which was summarized by Nathanson as affect is biology, feeling is psychology, and emotion is biography [8]. Given the lack of consensus on distinctions between "affect" and "emotion" and to align with the field of studying the neurobiology of emotion, known as "affective neuroscience", we will preferentially use the term "affect" but recognize that the two terms may be used similarly.

From an affective neuroscience perspective, "affect" may be defined as "an evoked response to an environmental stimulus with motivational salience" [9]. Motivational salience may be parsed into two orthogonal dimensions: (1) "valence" and (2) "arousal". Valence refers to whether a stimulus is appetitively rewarding [positive valence] or aversive [negative valence]. Arousal refers to the amount of an organism's resources, such as energy, that are mobilized in response to a stimulus. In turn, "affect regulation" has been defined by Thompson as the "extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions, especially their intensive and temporal features, to

accomplish one's goals" [10]. To amplify several aspects of this definition, affect regulation is not just dampening or suppression of negative emotion (such as anger), but rather the dynamic balance between positively- and negatively-valenced emotions which can involve increasing or decreasing the elicited arousal [11]. Moreover, affect regulation involves processes within the individual, both conscious and unconscious, as well as external influences, such as input from caretakers and experience from prior experiences with others. Lastly, affect regulation is not a solitary process that follows a one-way sequence from emotion to its regulation [12]. Instead, affect regulation requires the interplay between many separable sub-processes, such as attention and processing of emotional stimuli, memory for prior events, response to rewards and punishments, and decision-making.

To exemplify these constructs consider the scenario of a child tasting some chocolate ice cream (stimulus). The child finds the ice cream very positively rewarding (affect; moderate arousal, positive valence). The child is aware that the ice cream tastes good (feeling), and s/he giggles remembering the last time s/he had ice cream (emotion). The child then goes to obtain more ice cream (affect regulation).

It is beyond the scope of this manuscript to fully describe all of the brain/behavior interactions underlying the sub-processes of affect regulation, as innumerable manuscripts, presentations, and entire books have attempted this. However, we would like to discuss several that seem germane to BD.

By definition, affect regulation begins with the detection of an environmental stimulus and categorizing it. For example, is that a lion that I should avoid, or a housecat that I should pet? Is mom or dad happy … or angry? Making these determinations of object identity involves the fusiform gyrus, occipital cortex, and superior temporal gyrus among others [13]. These regions are categorize stimuli as animate or inanimate, and moving or not moving. Importantly, these regions seem especially geared to process faces, which are among the most important emotional stimuli in humans [14–18].

The recognition of facial emotions is another sub-process of affect regulation. It can be probed using computerized behavioral tasks on their own, or in conjunction with magnetic resonance imaging (MRI), whereby participants must identify the emotion (e.g., happy, sad, angry) displayed by an actor. In addition to the above regions involved in stimulus detection and categorization, the amygdala has also been implicated in processing facial emotions. Many studies have linked the amygdala to negatively-valenced emotionally stimuli. For example, surgical resection of the amygdala results in impaired recognition of facial expressions of negatively-valenced emotions, such as fear and sadness, but not of positively-valenced emotions, such as happiness [19;20]. Compared to adults, adolescents have greater amygdala activation to negatively-valenced emotional expressions, including fear, vs. neutral stimuli [21–23]. Moreover, there is a significant association between increased activation to fearful or threatening faces and the short variant of the serotonin transporter gene which is thought to convey susceptibility for depression and anxiety [24]. Nevertheless, studies have also linked the amygdala to the processing of positively-valenced emotional stimuli. For example, functional MRI studies have demonstrated increased amygdala activation to happy vs. neutral faces in adult controls [25].

Also by definition, affect regulation involves response to rewards (appetitive, pleasurable, positively valenced stimuli) and punishments (aversive, painful, negatively-valenced stimuli). For example, do I finish my homework after I arrive home from school because it will make me happy? My parents happy? To get the 50 cents I was promised? To avoid getting my parents mad? If I do not do my homework, and my parents get mad, will I learn and tomorrow complete my homework when I arrive home from school? From an affective neuroscience perspective, response to rewards and punishment is integral to our understanding of BD, given clinical symptoms that potentially suggest mania to be a hyper-hedonic period involving excessive goal-directed activity, involvement in pleasurable activities with high potential for painful consequences, and grandiosity, whereas depression may be a hypo-hedonic period involving anhedonia, worthlessness, and hopelessness. It appears that these behavioral/emotional manifestations of mood disorders are linked to three functionally connected brain regions involved in processing rewards and punishments: (1) the prefrontal cortex (PFC), (2) the amygdala, and (3) the striatum [26–29].

One example of the myriad sub-processes of affect regulation that involve response to rewards and punishment is cognitive flexibility, meaning the ability to adapt one's thinking and behavior in response to changing environmental conditions, including rewards [30;31]. In the lab, cognitive flexibility may be tested using reversal learning tasks, whereby participants try to win as many points possible by first learning, through trial-and-error, which of two objects is rewarded (wins points) and which is punished (loses points) in order to stick with the rewarded stimulus. Then, without warning, the stimulus-reward association is reversed—i.e., the previously rewarded stimulus is now punished, and the previously punished stimulus is now rewarded. For example, if a dog and cat are presented, through trial-and-error, the child figures out that the dog is rewarded initially. After a number of trials of successfully winning points by picking the dog, the child switches to now win points by picking the cat once the dog starts losing points.

Reversal learning is mediated by a distributed circuit encompassing: (1) the prefrontal cortex (PFC), including the orbitofrontal cortex, which mediates the reversal of stimulus-reward relationships [30–32], (2) the striatum, including the accumbens area, caudate, and putamen, which transforms concrete stimulus-exemplar information into motor responses [30;33], and (3) the amygdala, which encodes the salience of rewards and punishments [27;34]. Moreover, Blair et al. suggest that reversal learning and the OFC tap into the regulation of aggression [35–38]. In particular, the OFC has been linked to social response reversal, whereby people react to others' negatively-valenced emotional states, such as anger, by displaying aggression, including frustration and irritability.

Two additional and related sub-processes of affect regulation are attentional control and conflict monitoring. To illustrate these related processes, do I direct my attention to the teacher at the head of the class, or the student whispering next to me? Attentional control refers to the top-down process of devoting attentional resources and planning to stimuli and is most often linked to the dorsolateral PFC (DLPFC) [39–41]. Conflict monitoring refers to the process of adjusting behavior to override one response in favor of another and is most often associated with the anterior cingulate cortex (ACC) [42]. Attentional control can be tested by tasks involving planning, problem-solving, and executive function. Conflict monitoring can

be tested by tasks such as the Stroop paradigm, whereby participants have more difficulty with incongruous stimuli (e.g., reading the word "RED" printed in blue ink) than control items (e.g., the word "RED" printed in red ink) [43]. Go/No-go paradigms are also used to probe conflict monitoring and response inhibition, whereby participants are instructed to press a button as fast as they can if they see a word (e.g., "ZEBRA") but to not press if they see a non-word (e.g., "QWERT"). Most trials on a go/no-go task are go responses (words), so that pressing the button becomes the "prepotent" response, with not pressing (to non-words) requires response inhibition.

AFFECT REGULATION IN TYPICAL DEVELOPMENT

What do we know about affect regulation in typically-developing children and adolescents? The field of affective neuroscience aims to answer this question using a number of techniques, including behavioral experiments, neuroimaging, genetics, and temperament.

From infancy, affect regulation begins as the interplay between interactions with caregivers and an infant's temperament, the latter of which includes individual differences in (a) reactivity [the speed and intensity of emotional activation] and (b) self-regulation [the capacity to modify the intensity and duration of an emotion through behaviors, such as self-sucking or approaching/avoiding contact with caregivers] [44;45]. Such early affect regulation can be observed and studied using constructs, such as, behavioral inhibition [the tendency of a child to become fearful and withdraw from novel situations] [46]. With time, cognitive development and emotional experience enable the infant to exert greater affect self-regulation [47]. Affect regulation is inherited to some degree, as demonstrated by identical twins performing more similarly than fraternal twins on parental reports of emotion regulation [48;49].

Adolescence is also a time of great change, including not only physical changes and growth but also the development of the many sub-processes of affect regulation. Paradoxically, adolescence involves both greater ability to self-regulate as well as greater tendency to engage in risk-taking behavior, including driving, unprotected sex, and experimentation with illegal substances [50]. Recent longitudinal structural MRI studies have demonstrated that as children become young adults there is a loss of cortical gray matter in prefrontal and temporal cortices and increase in white matter volume [51;52]. Functional MRI (fMRI) studies have shown that age-related changes in recruitment of the PFC during tasks of working memory, response inhibition, and verbal fluency [53–57]. With all of this change and development, how does affect regulation account for the seeming inconsistency between adolescence as a time of cognitive development and a time of increased risk-taking? Recently, Casey has proposed a neurobiological model of adolescence to account for these inconsistencies. According to this model, during adolescence affect regulation represents a dynamic balance between (a) bottom-up processing of rewards by sub-cortical limbic regions, including the amygdala and accumbens area, and (b) top-down processing of cognitive control by the prefrontal cortex, with limbic structures maturing earlier than the PFC [58].

AFFECTS IN BIPOLAR DISORDER: KEY QUESTIONS

(A) IRRITABILITY

While irritability is one of the most common symptoms spurring parents to bring their children and adolescents for psychiatric treatment, the diagnosis and treatment of irritability remains a major challenge for clinicians and researchers alike. In part, this is due to the fact that irritability is a non-specific symptom in current psychiatric nosology. Irritability is an explicit DSM-IV-TR diagnostic criterion for a manic episode, generalized anxiety disorder, post-traumatic stress disorder, and, for children or adolescents, for a major depressive episode. Irritability is an associated symptom for pervasive developmental delay-spectrum disorders (autism, Asperger's), attention deficit hyperactivity disorder (ADHD), and oppositional defiant disorder (ODD) [59].

Despite its inclusion in the above diagnoses, there is no widely accepted definition of irritability. Moreover, there is no uniform assessment measure of irritability, as standardized diagnostic interviews used both clinically and in research use different prompts to probe for irritability [60]. For example, irritability is defined as: (a) "anger; crankiness; bad temper; short-tempered; resentment or annoyance, whether overtly expressed or not; easily lose temper; touchy or easily annoyed" (Child Schedule for Affective Disorders [KSADS]) [61], (b) "cranky; angry toward people you had no reason to; talk back; temper tantrum" (Diagnostic Interview Schedule for Children [DISC]) [62], and (c) "grumpy, crabby, talked back, sassy, wouldn't do something your parents asked you to do" (Children's Depression Rating Scale [CDRS]) [63]. Thus, the challenge for all those involved is to determine whether the irritability is a manifestation of normal childhood or adolescence, or if it is a symptom of an underlying psychiatric disorder, including BD [64].

Moreover, there is no solitary biological cause of irritability, whether brain region, neurotransmitter, or gene. The brain region most frequently implicated is the orbitofrontal cortex (OFC), dating back to notable case reports such as Phineas Gage, whose personality was transformed from good-natured and hardworking to angry and labile after an iron tamping rod was blown through his skull and OFC, as shown by modern reconstruction of the incident [65]. Imbalances in virtually every major neurotransmitter, including serotonin, glutamate, GABA, and catecholamines, also play a role [66]. Moreover, recent studies have begun to explore the link between irritability and genotype related to these neurotransmitters [67;68].

(B) EUPHORIA

While irritability is a non-specific, yet impairing, symptom of BD, the elevated and expansive mood (euphoria) found during mania is a specific symptom of BD. From an affective neuroscience perspective, euphoric mania may represent a hyper-hedonic period of increased responsivity, or seeking out, of rewards. In BD adults, this position is supported from several lines of research. From a temperament perspective, two studies have found that those with history of mania, although in remission, are more likely to endorse items reflecting perfectionism and the need to achieve goals including "If I try hard enough, I should be able to excel at anything I attempt" [69;70]. Moreover, a longitudinal study using the

Behavioral Inhibition System Behavioral Activation System (BIS/BAS), a scale designed to measure individual differences in the avoidance of punishment (BIS) or approach towards reward (BAS) [71], has shown that BAS hypersensitivity (i.e., hypersensitivity to rewards) predicted shorter time to onset of manic and hypomanic episodes [72]. Neuroimaging studies also support the potential alteration in reward processing in BD adults, with a recent study showing that whereas schizophrenic or control adults have activation of dopaminergic brain areas, including ventral tegmentum areas, to the expectation of monetary rewards and accumbens area to receipt vs. omission of rewards, manic BD adults did not [73]. Moreover, genetic studies have demonstrated that carriers of the short (S) polymorphism of the serotonin transporter gene has been associated with an increased risk for anti-depressant associated mania in BD adults [74].

(C) DEPRESSION

Whether called "bipolar disorder" or "manic-depressive illness", BD is not just about mania, as it involves depression, too. As is the case with irritable and euphoric mania, we know far more about depression in BD adults than in minors. In adults, only 25–33% of those with lifetime history of mania deny episodes of depression [75]. Moreover, several large prospective studies have shown that BD adults often spend more time depressed than manic in approximately a 3:1 ratio [76]. For example, Post et al. showed that of 258 BD adults followed prospectively for one year spent 33.2% of their time depressed while only 10.8% manic [77]. Anger attacks were more common in depressed BD adults (62%) than those with unipolar depression (26%) [78].

With respect to pediatric patients, there are several important questions. For example, do BD youth spend the majority of their time depressed as has been shown in BD adults? If not, does this potentially reflect differences in affect regulation? Also, can treatments resolve the depression found in PBD, given the risk for medication induced mania, especially with serotonergic medications? At present, there is a great need to understand the neurobiology of depression in PBD subjects.

AFFECT REGULATION IN PEDIATRIC BIPOLAR DISORDER

Against this backdrop of the basics of affect regulation in normal development and in BD, what do we know about affect regulation in PBD? The short answer is that the past 8–10 years have seen great progress in PBD research. However, there is still a great deal to learn about the pathophysiology, phenomenology, and treatment of PBD, and this work is being conducted at a number of sites around the country and worldwide.

Returning to the abovementioned sub-processes of affect regulation, several studies have evaluated face processing in PBD. Several of these have used the Diagnostic Analysis of Non-Verbal Accuracy (DANVA), which requires participants to view and to categorize sets of child and adult faces displaying high- and low-intensity expressions of happiness, sadness, anger, or fear [79]. These studies have shown that PBD youth were significantly more likely to miscategorize child images of happy, sad, and fear as angry compared to minors with either anxiety disorders or controls [80]. A second study found that an expanded sample of PBD participants made more errors on child and adult faces than an expanded

sample of controls, with secondary analyses suggesting that PBD participants were less sensitive to anger and happiness in children's faces and less sensitive to anger and sadness in adults' faces than controls [81]. Functional neuroimaging studies have followed up on these behavioral studies. PBD youth had greater activation of the amygdala and striatum than controls when they were attending to emotional aspects of faces [82]. These same PBD youth had greater neural activation in the striatum and ACC when successfully encoding happy faces into memory, and greater activation of the OFC when successfully encoding angry faces into memory [83].

Specifically in regard to cognitive flexibility, studies have shown that PBD participants are impaired versus typically-developing controls on reversal learning tasks. PBD youth make more errors, require more trials to achieve minimal competence, and require more time to complete the simple reversal stage of the intra-dimensional/extra-dimensional shift task (IDED), a computerized version of the Wisconsin card sorting task (CANTAB, Cambridge UK) [84]. Four prior studies found similar results in BD adults with this task in both mania and euthymia, suggesting this may be a trait deficit in BD, rather than a mood-state dependent phenomenon [85–88]. In a separate study, PBD participants made more errors than controls on a probabilistic response reversal task (PRR) that further manipulates reward and punishment by adding probabilistic trials (e.g., for stimulus pair dog/cat, during initial acquisition trials, dog is rewarded 80% and punished 20% while cat is rewarded 20% and punished 80%; subsequent reversal trials have dog rewarded 20% and punished 80%, while cat is now rewarded 80% and punished 20%) [89;90].

Studies of attentional control and conflict monitoring have demonstrated the following. Using a Stroop color-naming task, PBD adolescents had increased activation in the left putamen and thalamus during incongruent (the word "BLUE" written in red ink) versus congruent (the word "BLUE" written in blue ink) trials [91]. Using a stop-signal task that required participants to inhibit a pre-potent motor response, PBD participants had a reduced striatal "error signal" (thought to cause avoidance of similar mistakes on subsequent trials) during failed motor inhibition compared to controls [92]. In a related study that used a change-signal task requiring participants to inhibit a prepotent response and substitute an alternative response, PBD participants had significantly more neural activation in the DLPFC and primary motor cortex than healthy controls during correctly performed change trials versus correctly performed go trials [93].

Several important studies have begun to address the controversy regarding irritability vs. euphoria in PBD. While there is no rating instrument that is sensitive and specific for irritability found in BD, a consensus has emerged that the development of such an instrument is vital. In this regard, the K-SADS Mania Rating Scale is designed to measure mania in children, and unlike other measures, has specific anchors for the irritability item [94]. However, many assert that it is unlikely that a single item can capture the complexity of irritability in PBD [60;95]. For example, more than 50% of consecutive adolescents admitted to an inpatient psychiatric unit were judged to have moderate to severe irritability using the K-SADS Mania Rating scale, but the consensus diagnoses given to each of these admitted adolescents were quite varied [96]. Ongoing PBD studies from around the country report high rates of irritability in their samples, but differing rates of euphoria. The Course and Outcome

of Bipolar Youth (COBY; 3 sites University of Pittsburgh, Brown University, UCLA) found that 84.5% of their BD type I youth (N=220) had irritability or anger and 91.8% had elevated or expansive mood during their most severe lifetime manic episode [97]. The research group at Massachusetts General Hospital found that of N=86 PBD subjects, 94% irritable mood while only 51% had euphoria [98]. Geller et al. at Washington University in St. Louis found that of N= PBD subjects, 97.9% had irritable mood while 89.3% had elated mood [99].

Leibenluft has proposed a classification system of PBD to facilitate research about irritability vs. elation in PBD [100]. At the heart of this system a definition of irritability grounded in affect regulation that consists of "marked reactivity to negative emotional stimuli manifest verbally or behaviorally—i.e., temper tantrums out of proportion to the inciting event and/or child's developmental stage occurring >3 times per week during the past 4 weeks". Building upon this definition, "broad phenotype" youth (also known as "severe mood dysregulation" [SMD]) have functionally-impairing (1) irritability (as defined above), (2) baseline sad or angry mood, and (3) hyperarousal (3 of insomnia, agitation, distractibility, racing thoughts/flight of ideas, pressured speech, or intrusiveness) that are chronic and non-episodic (symptoms present for 12 months without 2 months symptom free). These SMD youth do not have euphoria, and they do not have distinct mood episodes. At the other extreme, "narrow phenotype BD" (NPBD) youth have (1) clearly defined episodes of euphoric mania accompanied by 3 DSM-IV-TR "B" symptoms of mania and (2) symptoms of euphoric mania must be present for most of the day, every day for 4 days for hypomania or 7 days for mania. Thus, NPBD and SMD groups are orthogonal to one another, to separate out issues of irritability vs. euphoria and chronic course vs. distinct episodes that have been controversial in PBD [101;102].

Studies probing differences in affect regulation using these constructs are in their early stages. Thus far, epidemiological samples of children have shown that SMD may have a prevalence of 3.3% among those 9–19 years, although when these same youth are followed into adulthood, they were significantly more likely to be diagnosed with unipolar depression than those without SMD [103]. Several lines of ongoing research are probing the brain/behavior interactions mediating affect regulation in NPBD vs. SMD youth, including the processing of emotional faces and also processing of rewards/punishments. With respect to face processing, both NPBD and SMD youth required greater emotion intensity to correctly identify facial images (including those of happiness, surprise, fear, sadness, anger, and disgust) compared to controls [104]. Moreover, NPBD and SMD youth made more errors in the identification of facial emotions than from those with anxiety and/or depression, those with ADHD and/or conduct disorder, and controls [105]. With respect to rewards and punishments and to cognitive flexibility, while both NPBD and SMD youth performed worse than controls on the compound reversal stage of the intra-dimensional/extra-dimensional set shifting task (IDED), NPBD youth were specifically impaired on the simple reversal stage vs. both SMD and controls [106]. The same study also demonstrated that NPBD youth performed worse than both SMD and controls on a task requiring subjects to inhibit a prepotent motor response and substitute a new response (i.e., press "1" if you see an "X", press "2" if you see an "O", and press "3" if you see a blue square after either an "X" or "O" are presented). In contrast, there was no difference between NPBD and SMD youth in decision-making task requiring subjects to select from differentially rewarded and punished

stimuli [107]. In an attempt to study differential response to frustration elicited via rigged feedback, a recent electrophysiology study found that, while both NPBD and SMD youth reported more arousal than controls, NPBD subjects had lower P3 event-related potential (brain wave) amplitude than either, reflecting impaired executive attention, whereas SMD youth had lower N1 event-related potential amplitude than either NPBD or controls during both frustration and non-frustration events, suggesting impaired initial orientation [108]. In a separate study, there was no difference between NPBD, SMD, and controls in magnitude of startle response during reward, punishment, or neutral conditions [109].

THE FUTURE

In summary, the past 8–10 years have shown great progress in what we know about affect regulation, including the brain/behavior interactions that differentiate PBD youth from those typically-developing youth without psychopathology. Affective neuroscience techniques, such as behavioral tasks, neuroimaging, and electrophysiology and event-related potentials, have advanced what is known about affect regulation in PBD. In particular, these studies have shown that PBD involves alterations in several sub-processes involved with affect regulation, including emotional face processing, cognitive flexibility, and response to reward and to punishment. These deficits are mediated by alterations in several brain regions, including a distributed neural circuit encompassing the PFC, striatum, and amygdala. Ongoing and future studies will examine the diagnostic specificity of such impairments versus other psychiatric disorders. They will also probe the relationship between such processes and underlying neural, genetic, and developmental mechanisms and mediators. Lastly, they will evaluate the potential for treatments, including medications and/or computerized tasks, to improve affect regulation in children and adolescents with BD. More and more, the future will likely involve the integration of affective neuroscience into clinical practice.

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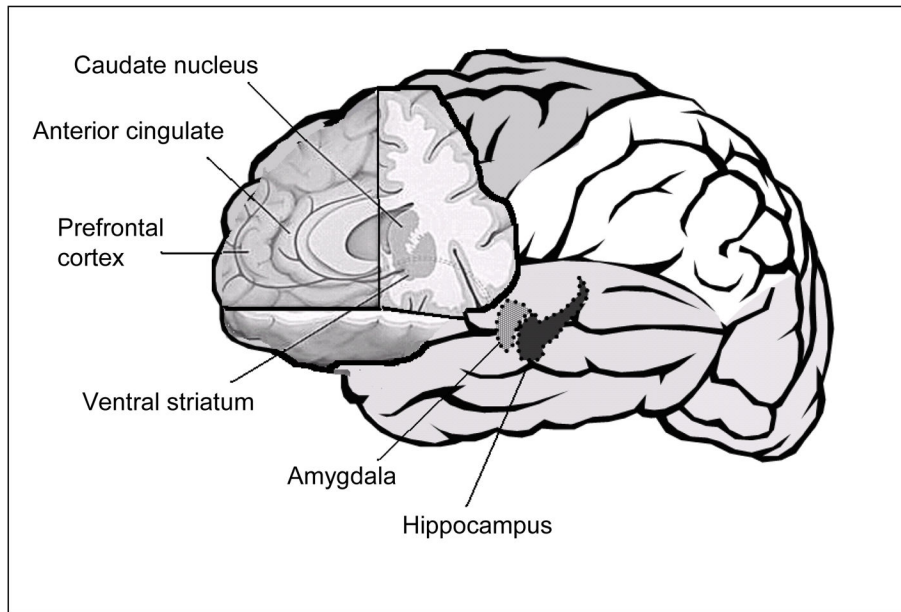
Figure 1.
Brain Regions Implicated in Affect Regulation

Table 1

Affect Regulation in Pediatric Bipolar Disorder

Function/Task	Study (author, year)	Major Finding:
Face/Emotion Processing	McClure EB et al. 2003	PBD youth more likely to mis-categorize happy, sad, fearful faces compared to anxious and control youth
	McClure EB et al. 2005	PBD youth less sensitive (does this mean more errors?) to angry/happy child faces and angry/sad adult faces than controls
	Rich BA et al. 2006	Greater amygdala/striatum activation when processing emotional faces in PBD youth than controls
	Dickstein DP et al. 2007	Greater ACC/striatum activation when encoding happy faces and greater OFC activation when encoding angry faces in PBD youth compared to controls
	Rich BA et al. 2008	NPBD and SMD youth required higher intensity of emotion to correctly identify emotional faces
	Guyer AE et al. 2007	NPBD and SMD youth made more errors identifying emotions compared to anxious, depressed, ADHD, CD, and control youth
Cognitive Flexibility - Reversal Learning	Dickstein DP et al. 2004	PBD youth made more errors and required more trials/time on reversals compared to controls
	Gorrindo T et al. 2005	PBD youth made more errors on probabilistic trials compared to controls
	Dickstein DP et al. 2007	NPBD youth performed worse than SMD and controls on reversal trials, with SMD performing worse than controls
Attentional Control and Conflict Monitoring	Blumberg HP et al. 2003	Greater activation in left putamen and thalamus during incongruent trials compared to congruent trials of the Stroop Task
	Leibenluft E et al. 2007	Reduced striatal activation during failed motor inhibition in PBD versus controls on the Stop-signal task
	Nelson EE et al. 2007	Greater activation in DLPFC and primary motor cortex when correctly inhibiting a pre-potent motor response and executing an alternative response in PBD youth versus controls
Response to reward and punishment	Rau G et al. 2008	No difference in performance on reward decision-making task between NPBD and SMD
	Rich BA et al. 2007	NPBD and SMD showed more arousal compared to controls during frustration and non-frustration events
Electrophysiology/ERP response to reward and frustration.	Rich BA et al. 2005	No differences in magnitude of arousal found between NPBD, SMD, and controls during reward, punishment, or neutral conditions.