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Emotional dysregulation and Attention-Deficit/Hyperactivity Disorder

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Abstract

It has long been recognized that many individuals with ADHD also have difficulties with emotion regulation but lack of consensus on how to conceptualize this clinically challenging domain renders a review timely. The authors examine the current literature using both quantitative and qualitative methods. Three key findings emerge. First, emotion dysregulation is prevalent in ADHD throughout the lifespan and is a major contributor to impairment. Second, emotion dysregulation in ADHD may arise from deficits in orienting towards, recognizing and/or allocating attention to emotional stimuli; these deficits that implicate dysfunction within a striato-amygdalo-medial prefrontal cortical network. Third, while current treatments for ADHD often also ameliorate emotion dysregulation, a focus on this combination of symptoms reframes clinical questions and could stimulate novel therapeutic approaches. Three models to explain the overlap between emotion dysregulation and ADHD are considered: emotion dysregulation and ADHD are correlated but distinct dimensions; emotion dysregulation is a core, diagnostic feature of ADHD; and the combination constitutes a nosological entity, distinct from both ADHD and emotion dysregulation alone. The differing predictions from each model can guide future research into this much-neglected population.

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Keywords

Attention Deficit hyperactivity disorder; emotion; affect; irritability; cognition; meta-analysis

Introduction

It has long been recognized that emotion dysregulation is common in individuals with neurodevelopmental disorders, including Attention-Deficit/Hyperactivity Disorder (ADHD). Indeed, in the early conceptualization of ADHD as reflecting 'minimal brain damage', emotion dysregulation was placed above inattention among the cardinal symptoms (1). Only by DSM-III did emotional symptoms became an 'associated feature' rather than a diagnostic criterion of ADHD. Renewed interest in this overlap makes a review timely. Here, we consider the overlap of emotion dysregulation with ADHD, focusing on prevalence, pathophysiology and treatment.

In line with previous theorists, we define emotion regulation as an individual's ability to modify an emotional state so as to promote adaptive, goal-oriented behaviors (2). It encompasses the processes that allow the individual flexibly to select, attend to, and appraise emotionally arousing stimuli. These processes trigger behavioral and physiological responses that can be modulated in line with goals. Emotion dysregulation arises when these adaptive processes are impaired, leading to behavior that defeats the individual's interests. We define it as encompassing; emotional expressions and experiences that are excessive in relation to social norms and context-inappropriate; rapid, poorly controlled shifts in emotion ('lability'); and the anomalous allocation of attention and to emotional stimuli. Here, we focus on the clinical expression of emotional dysregulation as irritability, which is often linked with reactive aggression and temper outbursts (3-5).

Emotion dysregulation is a dimensional trait that is not unique to ADHD; rather, it undercuts the traditional divide between internalizing and externalizing diagnoses and indeed may partly explain their high correlation (6). For example, a study which contrasted 105 irritable, emotionally dysregulated children with ADHD against 395 non-irritable ADHD children found increased rates not only of Oppositional Defiant Disorder but also Depression and Dysthymia (7).

Emotion dysregulation is also not synonymous with any single DSM-5 disorder. For example, of the three symptoms clusters in Oppositional Defiant Disorder-angry/irritable mood, defiant behavior and vindictiveness- only the first plausibly reflects dysregulated emotions (8). In its extreme form, emotion dysregulation is likely to emerge as a major etiological factor behind the frequent, severe temper outbursts and irritability of the new DSM-5 diagnosis, Disruptive Mood Dysregulation Disorder. However, emotion dysregulation is a dimensional entity, not a categorical diagnosis, and here we consider the full spectrum of emotion dysregulation within ADHD, not just extremes. We thus include individuals with emotion dysregulation who do not meet criteria for any DSM diagnoses beyond ADHD.

We focus on emotion dysregulation itself, rather than on diagnoses that may include emotion dysregulation and be comorbid with ADHD. We do so because it is a simpler symptom construct that is familiar to clinicians and, consistent with the Research Domain Criteria initiative, may be more readily tied to underlying neurobiological mechanisms.

Methods

We conducted a literature search for relevant articles published before January 1st 2013 (details in Supplementary Material). Studies were categorized according to topic: (1) prevalence; (2) pathophysiology; and (3) treatment. Quantitative syntheses using pooled effect sizes were possible for studies of three related literatures: aggressive behavior (9-20), emotion recognition (12, 21-36) and delay aversion (35, 37-50). Remaining studies were reviewed qualitatively.

Section 1: Prevalence

Childhood—Most epidemiological research has focused on children and finds a strong association between ADHD and emotion dysregulation (35, 51-56)(Table 1). A population study of 5326 youth found mood lability in 38% of children with ADHD, a ten-fold increase over population rates (51). Elevated rates were found in non-comorbid ADHD children and equaled the rates seen in children with non-comorbid Oppositional Defiant Disorder. Research on the Child Behavior Checklist 'dysregulation profile' based on parent-reported problems with mood and aggression in youth who also have attention problems, shows community rates of 1-5%, compatible with high rates of emotion dysregulation among those likely to have ADHD (57). Clinic-based studies in youth with ADHD report similar prevalence estimates of emotion dysregulation of between 24% to 50%.

Reactive aggression may reflect emotion dysregulation (5). Our meta-analysis found consistent elevation in aggressive behavior in ADHD versus non-ADHD populations, associated with a large effect size (1.92, CI 0.95 to 2.89) - Figure 1A. In the general population, the correlation is higher between aggression and hyperactivity-impulsivity (0.60-0.83) than between aggression and inattention (0.20-0.56) (6). In clinics emotion dysregulation is commonly associated with either symptom domain (52, 56).

Importantly, behaviors reflecting emotion dysregulation can be reliably provoked among those with ADHD using paradigms that induce frustration (Supplemental Table 1). Children with ADHD show more negative affect and temper outbursts than comparison subjects during challenging tasks. This consistency is notable as different paradigms and behavioral measures were employed.

Infancy and early childhood—Modest correlations (0.10-0.37) are reported between infantile temperamental characteristics such as being fussy, angry, or difficult to control, and ADHD arising later in childhood (58-62) (Figure 2 and Supplemental Table 2). A longitudinal study of 7,140 children, found that while temperamental emotionality at age 3 predicted comorbid ADHD and internalizing disorders at age 7, activity level predicted comorbid ADHD and Oppositional Defiant Disorder (63). A second longitudinal study found that infants who developed hyperactive symptoms alone did not differ

temperamentally from typical infants, whereas those who ultimately developed both ADHD and aggressive symptoms were uncooperative and irritable from infancy onwards (64). In short, a difficult early temperament with prominent negative emotionality is modestly linked with later ADHD combined with emotion dysregulation.

Longitudinal studies—Most studies following children with ADHD into adulthood have not considered emotion dysregulation *per se* but focused on DSM-IV diagnoses and find increased rates of adult disruptive and antisocial disorders and, less consistently, mood and anxiety disorders (65). One study defined emotion dysregulation as a moderate elevation (>1SD and <2SDs) on the combined Child Behavior Checklist subscales of Attention Problems, Aggressive Behavior and Anxious/Depressed subscales (66). Such emotion dysregulation in 79 children with ADHD was associated four years later with more psychiatric comorbidities, greater social impairment and ADHD persistence, compared to 98 subjects with ADHD without emotion dysregulation and 204 controls. A population-based study of 2076 children found that those matching the Child Behavior Checklist 'dysregulation profile', had increased rates of anxiety disorders and disruptive behavior disorders in adulthood compared to non-dysregulated children (67).

Adult studies—Earlier concepts of adult ADHD included emotion dysregulation as a defining feature (68). This has been supported to some extent by recent clinic-based studies reporting impairing emotion dysregulation in between 34-70% of adults with ADHD, although population based studies are needed (69-73)–Table 1. Aggressive behaviors are also prominent. In a population study contrasting 950 adults with diagnosed or likely ADHD against 20,000 unaffected adults, those with ADHD had higher self-ratings of interpersonal conflict and negative, conflictual social ties (69). Other cross-sectional studies have compared of adults who have remitted from their childhood ADHD against those who have not. In such a comparison, 55 adults with persistent ADHD showed higher rates of emotion dysregulation (42-72%, depending on specific symptoms) than 80 adults with remitted ADHD (23-45%), although both groups differed from healthy subjects (70). This suggests a degree of developmental coherence: as symptoms of ADHD improve, so may emotion dysregulation.

Impairment—The combination of ADHD and emotion dysregulation represents a major source of impairment. In a study of 1,500 children, emotional problems had a greater impact than hyperactivity and inattention on well-being and self-esteem (74). Individuals with ADHD and emotion dysregulation were significantly more impaired in peer relationships, family life, occupational attainment and academic performance than those with ADHD alone (75) and this held after controlling for comorbid disorders, including Oppositional Defiant Disorder (76).

In summary, emotion dysregulation is found in around 25-45% of children and between 30-70% of adults with ADHD. It represents a major source of impairment and presages a poor clinical outcome.

Section 2: Pathophysiology

We now consider psychological and neural processes that might underpin the overlap between ADHD and emotion dysregulation. Informed by recent models, we draw a distinction between (1) 'bottom-up' processes that support or influence emotion regulation and (2) 'top-down' processes, such as the allocation of attention to emotionally arousing stimuli (77, 78). Most studies reviewed this section have either excluded individuals with comorbid diagnoses including Oppositional Defiant Disorder or controlled for these comorbidities, ensuring the anomalies pertain to ADHD *per se* rather than other disorders (Table 2).

'Bottom-up' psychological mechanisms—We consider two processes affecting emotion regulation: orienting to emotionally salient stimuli and the evaluation of signals for reward. In order for emotion to be regulated, posterior attention systems must both detect salient stimuli and signal that control is needed (77, 79). Evidence suggests anomalies in early orienting to emotional stimuli in ADHD. In healthy individuals, affectively charged stimuli receive enhanced early sensory encoding, detectable by electrophysiological markers. Two studies found that this effect is reduced in adults with ADHD when viewing positive, though not negative stimuli (80, 81); this would be expected to cause over-perception of negative stimuli. These studies further linked these early processing deficits with self-rated emotional lability. Additionally, whereas the startle reflex is typically accentuated by precursive positive and attenuated by negative stimuli, this effect is lost in adults with ADHD, further evidence of abnormal early processing of emotional stimuli in ADHD (82). Likewise, the rapid and accurate recognition of emotions in human faces or voices is central to well-regulated behavior; emotional misperception is linked with aberrant emotional responses and misperception can itself result from emotion dysregulation (83, 84). Studies on emotion labeling find moderate impairments in ADHD, our meta-analysis giving an effect size of 0.65 (CI 0.48 to 0.81)–Figure 1B.

The evaluation of emotionally salient stimuli has also been studied in relation to the evaluation of signals for potential reward. A preference for small, immediate rewards over larger, delayed ones, even when such choice defeats one's own goals and desires, is held to be a hallmark of impulsivity, reflecting an aversion to delayed reward (85, 86). Our meta-analysis found that ADHD was also moderately associated with this preference (effect size of 0.6, CI 0.4 to 0.79), albeit with considerable heterogeneity in results (35, 37) (–Figure 1C. This style of reward processing can be construed as a contributor to emotion dysregulation as it may reflect anomalous activity in limbic regions pivotal in emotion processing. Equally, the preference for immediate, small rewards might also reflect failures in 'top-down' regulatory mechanisms such as the ability to hold longer-term goals in mind, or to exert cognitive control to suppress the arousing value of immediate incentives (78, 87, 88). Thus, anomalies in reward evaluation provides further, albeit indirect, evidence for dysregulation of emotion systems in ADHD.

'Top-down' regulatory processes—Parasympathetic response is considered one gauge of regulatory functioning (89). In typically developing children, autonomic nervous system function tracks the valence of emotional stimuli and task demands, with greater top down

regulatory activity when stimuli are negative rather than positive (89). In children with ADHD this ability to adjust top down regulation in response to different emotional stimuli was partially lost, based on physiological indicators of regulation.

Another way to assess the recruitment of regulatory resources is to consider the allocation of attention itself to emotional stimuli. Just as emotion regulation requires the ability to recruit autonomic responses, it also relies on the ability to direct attention towards or away from emotional stimuli so as to maintain emotional homeostasis or maintain focus on a goal (90). This ability can be assessed by incorporating an affective dimension into a cognitive paradigm. For example, in the emotional Stroop task, individuals must deflect attention away from the emotional properties, such as emotional expression, and attend to a non-emotional feature, such as eye color. This manipulation exacerbates the performance deficits already evident in ADHD suggesting that performance drops off more steeply than it does in typical individuals under emotional challenge (91, 92).

Finally, given that ADHD is associated with poor higher order cognitive control even in the absence of emotionally salient stimuli, what role does poor cognitive control play in emotion dysregulation in ADHD? Evidence suggests a modest connection but not isomorphism. For example, in 49 boys with and without ADHD, cognitive control, indexed by response inhibition, accounted for 11% of the variance in 'dysregulated' behavior during a frustrating task (93). A larger study of 424 children with ADHD and their siblings found that, while a range of neuropsychological variables correlated with emotional lability this link was not direct but mediated almost entirely by the severity of ADHD symptoms (37).

In summary, emotion dysregulation in ADHD may arise from deficits at multiple levels. These range from abnormal early orienting to emotional stimuli, particularly with regard to negative stimuli and reward valuation through an inability to recruit top-down regulatory effort or attention in response to emotional stimuli. Meantime, deficits in cognitive processes, including working memory and response inhibition may contribute to emotion dysregulation, but they do not seem to alone explain its presence in ADHD.

Neural mechanisms: Here, we again employ the division between regions mediating 'bottom-up' responses to emotional stimuli - specifically the amygdala, ventral striatum and orbitofrontal cortex- and 'top-down', cortical regions controlling the allocation of attentional resources in emotionally arousing contexts (77, 94). In ADHD, functional imaging studies have yielded disparate findings, possibly because of differences in tasks, sample characteristics and limited power to detect effects in smaller studies but nonetheless some themes emerge- Table 2 and Figure 3.

Amygdala activation during emotion processing has received some research attention in ADHD. The larger studies find amygdala hyperactivation in ADHD, during both the subliminal perception of fearful expressions and while subjects rated their fear of neutral faces, although results are mixed (24, 29, 95-98)-Table 2 and Supplemental Material. Amygdala hyperactivation has also been reported in ADHD during the processing of delayed rewards, perhaps consistent with the delay aversion found in some behavioral studies (38, 99-101). Deficits in early processing of visual emotional stimuli and in the

modulation of the startle reflex, described above, also suggest amygdala dysfunction in ADHD. These functional deficits align with reports of amygdala structural abnormalities in ADHD, including surface morphology and dopamine receptor density (102).

The orbitofrontal cortex, which has rich interconnections with the amygdala, thalamus and multiple cortical regions, is pivotal in emotion regulation and reward representations (77, 103). Some data suggest orbitofrontal anatomic anomalies (104) and abnormal activation during the anticipation and receipt of rewards in ADHD. There is also decreased connectivity between the amygdala and orbitofrontal cortex, reflected in a loss of the typical correlation between the volumes of these structures (102).

The ventral striatum is the third important 'hub' in the 'bottom-up' circuitry, partly by virtue of its role in mediating positive affect and reward processing (105). Functional neuroimaging studies find reduced ventral striatum responsiveness in ADHD during the anticipation (and receipt) of rewards, thus contributing to aversion to delay- Table 2. By examining brain activity at rest, two groups have reported in ADHD both increased functional connectivity between the ventral striatum and orbitofrontal/ventromedial prefrontal cortex and decreased connectivity between these regions and cortical attentional control regions (106, 107). Thus evidence suggests dysfunction in a network encompassing the amygdala, ventral striatum, and orbitofrontal cortex that processes emotional stimuli and is implicated in emotion regulation.

With regard to cortical regions, in healthy subjects the addition of an emotional dimension to cognitive tasks usually boosts 'top-down' prefrontal cortical activation (particularly in ventrolateral, medial prefrontal and anterior cingulate cortical regions) and diminishes subcortical activity (77). These patterns are partly lost in ADHD. Specifically, when negative stimuli are added to a working memory task, performance deficits in ADHD are associated with hypoactivation in prefrontal 'control' regions, including ventrolateral, orbitofrontal and medial prefrontal cortices. However, when positive stimuli are used, ADHD subjects show hyperactivation in these regions (91). Similarly, two independent studies using the emotional Stroop task found hypoactivation in ADHD in right medial and ventrolateral prefrontal cortex while processing negative distractors but hyperactivation in left medial prefrontal cortex while processing positive distractors (92, 108). Such work represents the first stage in charting the neural basis of dysregulated attentional control in ADHD in the presence of emotional stimuli.

In summary, emotion dysregulation in ADHD implicates dysfunction in the amygdala, ventral striatum and orbitofrontal cortex, which could be regarded as the 'bottom-up' contributor. Regions at the interface of cognition and emotion (medial and ventrolateral prefrontal cortex) may underpin the abnormal allocation of attention to emotional stimuli and could thus be regarded as the major 'top-down' contributor to emotion dysregulation within ADHD (Figure 2). Higher cortical centers involved in motor control (supplementary motor areas, motor cortex), monitoring for salient stimuli (temporoparietal junction, frontal operculum) and in shifting attention flexibly (frontal eye fields, intraparietal sulcus) may play a more indirect role (109). The exact balance of symptoms stemming from ADHD and emotion dysregulation within an individual may depend on the degree to which each neural

network or level is compromised. We predict that dysfunction at the cortical nexus between cognition and emotion (medial and ventrolateral prefrontal cortex) would be strongly associated with symptoms of both ADHD and emotion dysregulation. If however, an individual has dysfunction that is more focused in 'higher' more lateral prefrontal/parietal cortical regions, then in that individual symptoms of ADHD such as inattention would predominate over emotion dysregulation. Conversely, an individual with predominately (para) limbic dysfunction may exhibit mainly symptoms stemming from emotion dysregulation.

Etiological factors: It has been proposed that the combination of ADHD and emotion dysregulation defines a distinct genetic group. In support, one group found that the siblings of probands with both ADHD and emotion dysregulation also had significantly elevated rates of this combination, although this has not been replicated (52, 110, 111). The Child Behavior Checklist defined dysregulation profile is highly heritable (67%) (112) and studies have suggested candidate genes (113). Turning to environmental factors, high levels of parental criticism and hostility have been linked both with the development of conduct problems in children with ADHD, and with the development of childhood ADHD in preschoolers with behavioral problems (114, 115). A plausible hypothesis is that failures of parental emotion regulation, reflected by high expressed hostility contribute to the development of emotion dysregulation in children with ADHD.

Section 3: Treatment

The management of emotion dysregulation within ADHD presents formidable therapeutic challenges partly because clinical trials in ADHD either fail to assess change in emotion regulation or do so as a secondary outcome. Psychostimulants are highly effective in treating Oppositional Defiant Disorder comorbid with ADHD (meta-analyses given at http://www.nice.org.uk/CG72). However evidence for psychostimulant efficacy on emotion dysregulation within ADHD is more limited (Supplemental Table 3). Two randomized, placebo-controlled studies in children with ADHD found psychostimulants reduced emotional lability and irritability. In adults, several studies find that the beneficial effects of psychostimulants on emotion dysregulation parallel the improvement seen in hyperactivity and impulsivity. However, two randomized controlled trials comparing amphetamine against placebo found no beneficial medication impact on a broad range of emotional problems and some studies find amphetamine preparations increase irritability and lability (116).

Among individuals with ADHD, psychostimulants also improve emotion recognition (80), and normalize both the startle modulation by affective stimuli (82) and performance on the emotional Stroop task (92). This behavioral normalization is accompanied by normalization of underlying neural activity (80, 82, 92).

Among the non-stimulant treatments, improvement of emotion regulation on atomoxetine paralleled improvement in core symptoms of ADHD among adults (71). Mood stabilizers have yielded mixed results. A trial of lithium for children with severe mood dysregulation, most of whom had ADHD, was negative (117). However, a comparison of behavior therapy combined with either divalproex or stimulants found that the use of divalproex was more

efficacious in children with severe aggressive behavior, most of whom also had ADHD (118). A further study found that among 30 children with ADHD whose aggression did not respond to open-label psychostimulant treatment and behavioral therapy, the addition of divalproex resulted in significantly higher rates of remission compared to placebo (119). The use of atypical antipsychotic medications for the combination of ADHD, emotion dysregulation and aggression still lacks a clear evidence base.

While cognitive and behavioral psychotherapies have limited impact on core symptoms of ADHD, there is preliminary evidence that interventions which specifically target emotion dysregulation are efficacious, which we consider as a future direction for research (120, 121).

The available literature suggests the following treatment approach. Psychostimulant treatment of the core symptoms of ADHD is often linked to a beneficial effect on emotion dysregulation and should be considered the first line of treatment. Atomoxetine also appears effective for symptoms of ADHD and emotion dysregulation. Adjunctive behavioral modification in children is reasonable as this combination is effective in those with mixed internalizing and externalizing symptoms, many of whom will be emotionally dysregulated (51, 122). Group based psychotherapy in adults with ADHD which bolster emotion regulation skills show promise but require replication (121). Lacking an evidence base for second-line pharmacological approaches to emotion dysregulation in ADHD, treatment will largely be guided by the presence of comorbid illnesses. For example, for the patient with ADHD and depression, in whom emotion dysregulation is often prominent, serotonin reuptake inhibitors combined with psychostimulants is reasonable (123).

Section 4: Conceptual models

We now discuss three models, whose proponents can be characterized as 'lumpers', who view emotion dysregulation as an integral component of ADHD; 'splitters', who view the combination as defining a distinct entity; and 'diplomats' who view symptoms of ADHD and emotion dysregulation as correlated but ultimately dissociable dimensions (Table 3). Current evidence is insufficient to choose decisively among these models, partly because few studies have been designed to address specifically the question of why emotion dysregulation is so prominent in ADHD. However, this framework generates testable hypotheses that stimulate future research.

The first model posits that emotion dysregulation is a core, defining feature of ADHD that is as central to the disorder as hyperactivity, impulsivity and inattention and harks back to earlier conceptualizations of ADHD (124). Emotion dysregulation is seen as an expression of the same neurocognitive deficits that underpin other symptoms of ADHD, and Occam's razor dictates that it is unnecessary to invoke additional emotional processing deficits. The model is parsimonious and recognizes the close associations between cognitive and emotional regulation systems. However, as noted above, the overlap between ADHD and emotion dysregulation is far from complete: many with ADHD do not show impairing levels of emotion dysregulation (55-75% of children and between 30-70% of adults with ADHD). Additionally, the evidence for widespread (para) limbic dysfunction in ADHD, and associated deficits in emotional processes, might argue against a reductionist model of

emotion dysregulation in ADHD as another expression of purely cortico-striatal-cerebellar dysfunction. This model also predicts that treatments that ameliorate core symptoms would have an almost equal impact on emotion dysregulation, which seems to occur in adulthood, but less clearly in childhood.

The second model holds that the combination of ADHD and emotion dysregulation defines a distinct entity (110, 111). This model has been generated largely on the basis of genetic findings of familial co-segregation of ADHD and emotion dysregulation, although evidence on this point is mixed (52, 110). This model could imply both a distinct neurocognitive etiology and clinical course for those with the combination of ADHD and emotion dysregulation, a possibility that warrants further testing.

The third model holds that symptoms of ADHD and emotion dysregulation are distinct but correlated dimensions, each underpinned by partly overlapping but dissociable neurocognitive deficits. This model has much in common with the concept of multiple but overlapping pathways to ADHD (94, 109). This model is supported by the significant but modest correlations between symptoms of ADHD and emotion dysregulation reviewed earlier; the symptom domains commonly co-exist but are far from completely overlapping. Similarly, modest correlations have been reported between deficits in emotional processes – such as deficits in emotion recognition and frustration tolerance- and the executive dysfunction often held to be a core feature of the disorder (35, 37). Longitudinal data reviewed earlier also suggest modest links between the course of ADHD symptoms and emotion dysregulation in early childhood, and perhaps in adulthood, consistent with a model of correlated, but distinct symptom dimensions.

Future research directions

Phenomenology and pathophysiology

Refinement of the phenotype is needed, as emotion dysregulation in individuals with ADHD is likely to have a number of clinically important components, such as irritability and mood lability (4, 51). It will be important to operationalize each component, develop consensus measurement techniques, and perform longitudinal studies to define how the developmental trajectories of the components interact with each other and with the dimensions of ADHD. Pathophysiological studies should include individuals lying along the spectrum of emotion regulation abilities, but perhaps oversample those most at clinical need, lying at the extreme of dysregulation. Such work would allow direct links to be made between emotional dysregulation in ADHD and the underlying neural anomalies- a link that has been made in relatively few studies.

Future functional imaging studies should include a broad range of tasks of emotion regulation, defining the neural bases of the ability to reinterpret the meaning of emotional stimuli, the adaptive suppression of ongoing emotional responses and the ability to employ strategies such as distancing oneself from emotionally arousing materials (77). We predict that emotionally dysregulated individuals with ADHD would lose the coordinated increase of medial prefrontal/anterior cingulate cortex and altered amygdala activation that underpins many forms of emotion regulation.

To what extent do individuals with ADHD develop emotional dysregulation for different reasons than those with other disorders? Could ADHD-specific symptoms or cognitive aberrations be related to emotional dysregulation? 'Mind wandering' is one candidate cognitive mechanism. It is typically measured as interference in tasks of cognitive control and appears to be related to a failure to deactivate the so-called default mode network of the brain, a deficit also found in ADHD (125). Importantly, mind wandering appears to lead to transient dysphoric mood and vice versa (126). Testing the links between attentional lapses and emotion dysregulation, and the possible mediating role of the default mode network may be a promising research avenue.

There is evidence in ADHD of an altered structural and functional maturation of the prefrontal cortical regions that support 'top-down' emotion regulation (127). Could disrupted developmental trajectories be particularly pronounced among those both ADHD and impaired emotion regulation? Our model predicts a disruption to the white matter tracts such as the uncinate fasciculus that connect limbic regions including the amygdala, hippocampus and orbitofrontal cortex and these tracts can be assessed using diffusion tensor imaging.

Behavioral genetic data on twins could parse out the degree to which ADHD and emotion dysregulation share genetic or environmental risk factors. This could be achieved by re-analysis of existing data sets which include measures of irritability and other relevant traits. Studies of environmental risk factors have focused on familial characteristics but could also define the characteristics of a child's peer group that confer vulnerability to emotion dysregulation.

Treatment

Is a two-pronged pharmacological approach aimed at both the symptoms of ADHD and those of emotion dysregulation more effective than psychostimulants alone? This question is being examined among children with severe mood dysregulation (most of whom have ADHD) by trials that use both psychostimulants and serotonin reuptake inhibitors (clinicaltrials.gov NCT00794040; NCT01714310). The use of SSRIs is grounded in pre-clinical studies showing that the modulation of serotonergic tone impacts on the processing of emotionally charged stimuli and clinical studies showing efficacy in promoting emotion regulation in other disorders (128).

Other agents show promise. Postsynaptic alpha-2 adrenoceptor agonists such as guanfacine treat core symptoms of ADHD and oppositionality (129). In healthy adults, guanfacine reverses the bias to respond less accurately to negative compared to positive emotional stimuli, partly through boosting activation of the left dorsolateral prefrontal cortex (130). Given the interactions between the lateral prefrontal cortex and the ventral/medial prefrontal cortical regions linked to emotion regulation, guanfacine emerges as a potential 'emotion regulator' in ADHD. Modafinil, which inhibits dopamine and norepinephrine transporters and decreases Y-aminobutyric acid also shows promise as a treatment for ADHD (131). In healthy adults, modafinil decreases amygdala activation during the viewing of fearful stimuli and boosts prefrontal cortical activation during executive functions (132). Again, this profile points to a drug with possible benefit for ADHD and associated emotion

dysregulation. Dietary interventions can be considered as there appears to be benefit from omega-3-fatty acid supplementation in ADHD (120). Given that low levels of omega-3-fatty acids are associated with electrophysiological anomalies during emotion processing in ADHD, might emotion dysregulation in ADHD also benefit from supplementation (133)?

Which psychotherapies are promising? Cognitive therapy can help individuals with ADHD to recognize and label emotions accurately, to challenge emotions which are not context appropriate, and to cope with intense negative emotional reactions (121). These skills have been augmented with mindfulness training that promotes a nonjudgmental, present-centered focused awareness of emotions. This approach, derived partly from dialectical behavior therapy for disorders with prominent emotion dysregulation such as borderline personality disorder, is currently being assessed in adults with ADHD (68). Improving executive functions such as working memory and planning abilities helps core ADHD symptoms in adults, but future studies should also ask if these cognitive interventions also improve emotion regulation (121). Similarly, it has been argued that parent-led 'games' can boost a pre-schooler's executive skills and might prevent later ADHD (134, 135). Might such early intervention also promote emotion regulation?

What of interventions that target not just the individual with ADHD but their social context? For example, there is a strong rationale for family based interventions to decrease negative family dynamics and thus perhaps enhance emotion regulation in both the parent and child with ADHD (114). A novel approach leverages a child's peer group as a therapeutic ally (136). Children with ADHD often form cliques with disruptive others, and classroom interventions might promote alliances with less disruptive children who can perhaps better model emotion regulation.

Conclusion

Since Still described the 'morbid excitability' of children with ADHD, the presence of emotional dysregulation in ADHD has been well recognized. Recent advances in the behavioral, neuroimaging and genomic sciences hold the promise that our renewed focus on this overlap will result in an understanding of the underlying pathophysiological mechanisms and stimulate novel treatment approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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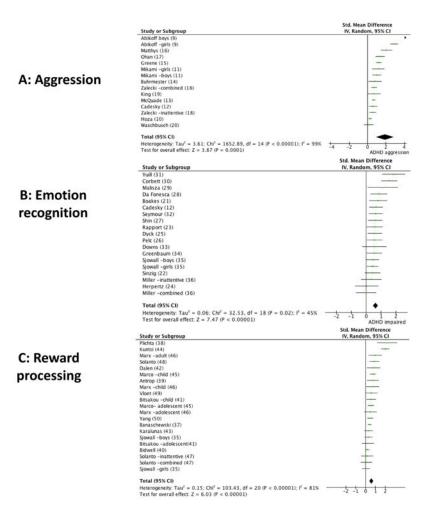
Figure 1.
Forest Plots With Standardized Mean Difference between the ADHD and control groups, effect size and homogeneity statistics are given. (A) Aggression: more aggressive behavior is seen in the ADHD groups (the effect size for the Abikoff study (ref 11) of boys was 14). (B) Emotion recognition deficits are seen in ADHD; (C) Reward processing here is measured by the tendency to immediate small rewards over larger, delayed ones. The ADHD participants show a tendency to prefer immediate, small rewards. Further details are given in Supplemental Material.

Study Author	Design	Early Temperament	Correlation	Outcome
Goldsmith et al 2004 (59)	*Longitudinal*	Anger (infancy)	0.14 * →	ADHD Symptoms (age 4)
		High approach (infancy)	0.19 * →	ADHD Symptoms (age 4)
Bates et al 1998 (60)	*Longitudinal*	Resistance to control (6 mo.)	0.30 ** →	Externalizing Symptoms (age 8)
Bates et al 1998 (60)	*Mixed design*	Resistance to control (6 mo.)	0.32 ** →	Externalizing Symptoms (age 8)
Carlson et al 1995 (61)	*Longitudinal*	Infant adaptability (3 mos.)	0.10 (NS) →	Hyperactivity (age 8)
			0.06 (NS) →	Hyperactivity (age 11)
Olson et al 2002 (62)	*Longitudinal*	Fussy/difficult (6 mos.)	0.01 (NS) →	Behavioral control (age 8)
			0.15 (NS) →	Inhibitory control (age 8)

Figure 2.
Correlations between infantile temperament and later externalizing and ADHD symptoms.
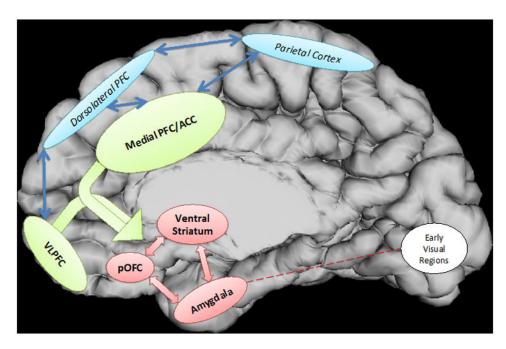Significance levels: *= $p<0.05$; **=$p<0.01$; NS= not significant.

Figure 3.
Neural circuits implicated in emotion dysregulation in ADHD. The circuitry which underpins deficits in early orienting to emotional stimuli and their perception is shown in red. Regions which interface between emotional and cognitive circuits, allocating attention to emotional stimuli are show in green. Circuitry implicated in cognitive control, motor planning and attention is shown in blue. (OFC=orbitofrontal cortex; VLPFC=ventrolateral prefrontal cortex; ACC= anterior cingulate cortex; PFC=prefrontal cortex).

Table 1

Prevalence estimates of emotional dysregulation in children and adults with ADHD. SD=standard deviation. RRR= relative risk ratio; ODD=Oppositional Defiant Disorder.

Study	Participants	Definition of 'emotional dysregulation'	Impairment criterion	Findings
Children and adolescents				
Stringaris et al 2009 (51)	Population based: N=5326	Parent and self report of emotional lability	Severity ratings of symptoms occurring 'a lot'	Parent rating of impairing emotional lability: ADHD alone: 38% (RRR= 12 compared to unaffected). ODD alone: 42% (RRR= 14.7). Self report: ADHD alone: 27% (RRR= 6.9) ODD alone : 14% (RRR=3.0)
Sobanski et al, 2010 (52)	Family based: ADHD N=216 Siblings N=142	Conners emotional lability index, parent and teacher ratings of: Unpredictable mood changes Temper tantrums Tearfulness Low frustration tolerance	3SD above population norms.	25% of ADHD probands had emotional lability >3SD above population norms
Anastopoulos et al 2011 (53)	Family based: ADHD N=216 Siblings N=142	Conners emotional lability index (see above)	Above the 65th percentile of population norms	Elevated levels: ADHD: 47% Unaffected: 15%
Spencer et al, 2011 (54)	Clinic based ADHD: N=197 Controls, N=224	Parent report of 'dysregulation profile based' on Child Behavior Checklist subscales of Attention Problems, Anxiety/ Depression and Aggression.	Scores 1-2 SD above norms. Above 2 SD, considered bipolar phenotype and excluded	ADHD: 44% with dysregulation profile. Controls: 2%
Sjowall et al 2012 (35)	Clinic based ADHD: N=102 Controls N=102	Parent report of child's ability to regulate specific emotions	Not given	ADHD showed significant impairment compared to controls in regulating all emotions
Strine et al, 2006 (55)	Population based: History of ADHD: N=512 No history of ADHD: N= 8169	On Strength and Difficulties Questionnaire, parent report of emotional and conduct problems, including Often loses temper Often unhappy (Also, Clingy, fearful, somatic complaints and having worries)	Parent rating of each symptom's impact.	Emotional problems: + history ADHD: 23% - history ADHD: 6.3%
Becker et al, 2006 (56)	Clinic based ADHD: N=1450	On Strength and Difficulties Questionnaire, parent report of emotional problems (see above)	Based on UK population norms	40% of boys and 49% girls had abnormally high levels of emotional problems.

Study	Participants	Definition of 'emotional dysregulation'	Impairment criterion	Findings
Adult studies				
Able et al, 2007 (69)	Population based (N=21000) Diagnosed ADHD, N=198 Likely ADHD, based on self-report scale, N=752 Controls, N=199	Self-report of tendency to become angry, disagree, or be critical of others Self report of degree to which others evoke feelings of anger	Not given	Both diagnosed and likely ADHD subjects more likely to express anger, to engage in conflict, and to have been the target of anger or intimidating behavior.
Barkley et al 2010 (70)	Clinic based ADHD: N=55 Controls: N=75	Self report of items reflecting emotional impulsivity (taken from the Behavior Rating of Executive Functioning)	Symptom occurs 'often'	Impatient: ADHD 72%, control 3% Quick to anger: ADHD 65%, controls 6% Easily frustrated: ADHD 85%, controls 7% Emotionally over-excitable: ADHD 70%, controls 6% Easily excitable: ADHD 73%, controls 14%
Reimherr et al 2005 (71)	Clinic based ADHD: N=536 (enrolled in treatment trials)	Self –report of items from the Wender-Reimherr Adult Attention disorder Rating Scale: Irritability and outbursts Short, unpredictable mood shifts Emotional overreactivity	2 SD above population norms	32% met criteria for emotion dysregulation
Reimherr et al 2007 (72)	Clinic based ADHD: N=47Enrolled in treatment trial	Wender-Reimherr Adult Attention disorder Rating Scale (see above)	2 SD above population norms	78% met criteria for emotion dysregulation
Surman et al 2013 (73)	Clinic based ADHD N=206 Controls N=123	Barkley's self-report scale Quick to anger, loses temper, argumentative, angry Easily frustrated, touchy Over-reactive emotionally, easily excited	Above 95th centile on population norms	55% of ADHD subjects met criteria for emotion dysregulation 3% of controls.

Table 2

Summary of fMRI studies into emotion perception, reward processing and the allocation of attention to emotional stimuli. TypDev= typically developing comparison group.

Study	Participants	Task	Behavioral results	fMRI results
EMOTION PERCEPTION AND RECOGNITION				
Brotman et al 2010 (95)	ADHD with no comorbidity (N=18) Severe mood dysregulation (N=29, 24 with ADHD) Bipolar affective disorder (N=43, 20 with ADHD) TypDev (N=37)	Rating of fear, nose width and passive viewing of neutral, fearful and happy and angry faces	Rating of fear in neutral faces: Severe mood dysregulation=bipolar > TypDev ADHD did not differ from any group	Left amygdala activity during fear ratings:- ADHD> TypDev= bipolar> severe mood dysregulation
Marsh et al, 2008 (96)	ADHD with no comorbidity (N=12) Callous-unemotional traits (N=12) TypDev (N=12)	Gender judgments on fearful, neutral and angry faces	No group differences in accuracy; ADHD had slower reaction times	Amygdala activity in ADHD during fear processing did not differ from TypDev.
Posner et al, 2011 (97)	15 ADHD – mix of medication naïve and receiving psychostimulants. Some had ODD (unclear number) 15 TypDev	Subliminal presentation of fearful face followed by supraliminal presentation of neutral expression on the same face. Post-scan face memory test	No group differences	Greater activity in medication naïve ADHD in amygdala and stronger functional connectivity with the lateral prefrontal cortex (BA47).
Herpetz et al, 2008 (24)	ADHD without comorbidity (N=13) Conduct disorder (N=22, 16 with ADHD) TypDev (N=22)	Passive viewing of negative, positive and neutral scenes	Conduct disorder rated emotional pictures as less arousing than did other groups.	Increased left amygdala activation in conduct disorder + ADHD, not ADHD alone. ADHD alone had decreased insula activation to negative faces
Schlochtermeier et al 2011 (98)	Adults treated in childhood for ADHD with no comorbidity N=10) Adults with childhood ADHD, medication naïve (N=10) TypDev (N=10)	Rating of positive and negative pictures	Adults with ADHD treated in childhood rated neutral pictures as more pleasant than medication naïve and TypDev	Decreased ventral striatum and subgenual cingulate activation in medication naïve adults with history of ADHD ADHD treated in childhood did not differ from TypDev
Malisza et al, 2011 (29)	ADHD (N=9) Autism (N=9) TypDev (N=9)	View happy and angry faces and respond to happy	Accuracy: Autism<ADHD=TypDev	ADHD had less fusiform, temporal poles activity than TypDev ADHD showed same amygdala activity as TypDev. Autism showed less amygdala activity than other two groups.
REWARD PROCESSING				
Strohle et al 2008 (99)	Adult ADHD without comorbidity (N=10) Controls (N=10)	Monetary incentive delay	No group differences	Decreased ventral striatum activation in ADHD during reward anticipation and increased orbitofrontal activation during reward receipt.
Plichta et al 2008 (38)	Adult ADHD without	Delayed discounting task (choose between	No group differences	Decreased ventral striatum activation in ADHD during

Study	Participants	Task	Behavioral results	fMRI results
	comorbidity (N=14) Controls (N=12)	immediate large or delayed smaller rewards)		processing of both immediate and delayed rewards. Within subjects, delayed reward in ADHD associated with increased activity of amygdala and caudate
Scheres et al 2007 (100)	Adolescent ADHD (N=11) Controls (N=11)	Monetary incentive delay	No group differences	Decreased ventral striatal activity in ADHD during reward anticipation
Stoy et al 2011 (101)	Adult ADHD (N=24) Analyzed as remitted vs persistent; and as history of childhood treatment with psychostimulants vs medication naïveControls (N=12)	Monetary incentive delay	No group differences	Decreased insula activation during outcome of loss avoidance in medication naïve adults compared to other groups.
Rubia et al 2009 (137)	Childhood ADHD on and off psychostimulants. One with comorbid ODD (N=13) TypDev (N=13)	Rewarded continuous performance task	No difference between medicated ADHD and TypDev; trend to worse performance in unmedicated ADHD	Unmedicated ADHD showed orbitofrontal hyperactivation during reward receipt, normalized by psychostimulants.
CONTROL OF ATTENTION TO EMOTIONAL STIMULI				
Passarotti et al 2010 (91)	Adolescent ADHD without comorbidity (N=14) Bipolar (N=23) TypDev (N=19)	Working memory task using angry happy and neutral faces	Accuracy- TypDev>ADHD>bipolar	ADHD vs TypDev: decreased decreased prefrontal and striatal activation to angry faces, increased to happy ADHD vs bipolar: similar cortical anomalies; more prominent subcortical anomalies in bipolar
Passarotti et al 2010 (108)	Adolescent ADHD without comorbidity (N=15) Bipolar (N=17) TypDev (N=15)	Emotional Stroop	Bipolar and ADHD slower than TypDev. More interference from positive distractors in bipolar and from negative distractors in ADHD.	For negative vs. neutral words:gradient of ventrolateral prefrontal cortical activation- ADHD<TypDev<Bipolar Both ADHD and bipolar showed more dorsolateral prefrontal and parietal activation than TypDev.
Posner et al 2011 (92)	Adolescent ADHD (N=15)- on and off psychostimulants TypDev (N=15)	Emotional stroop		Medication free ADHD showed edial prefrontal hyperactivity with positive and hypoactivity with negative distractors. Normalized on psychostimulants.

Table 3

Three models to explain the overlap between ADHD and emotional dysregulation are summarized with their predictions about clinical features, pathophysiology, and treatment.

	Phenomenology	Clinical course	Pathophysiology			Treatment
	Correlations between ADHD and emotion dysregulation		Psychological basis	Neural basis	Genetic	
Emotion dysregulation is integral to ADHD	Extremely high	Yoked clinical courses for symptoms of ADHD and emotion dysregulation	Deficits in behavioral inhibition and working memory mediate both core ADHD symptoms and emotion dysregulation	Anomalies confined to fronto-striatal-cerebellar circuits	Same genetic basis for ADHD + emotion dysregulation as ADHD	Treatments which improve ADHD will improve emotion dysregulation
Combined ADHD +emotion dysregulation defines a distinct entity	ADHD subgroup exists that is high on both symptom domains	Distinct clinical course in ADHD+emotion dysregulation from ADHD alone	Distinct cognitive deficits in ADHD+emotion dysregulation vs. ADHD alone.	Distinct neural basis for ADHD+emotion dysregulation vs. ADHD alone	Distinct genetic basis for ADHD+ emotion dysregulAtion vs. ADHD alone	Existing treatments for ADHD may be less effective for ADHD +emotion dysregulation
Symptoms of ADHD and emotion dysregulation are correlated but distinct dimensions	Modest	Similar but dissociable clinical course for symptoms of ADHD and emotion dysregulation	Deficits in emotional processing mediate dysregulation and correlate with deficits mediating core ADHD symptoms	Anomalies extend beyond fronto-striato-cerbellar circuits to (para) limbic regions.	Some genes shared between ADHD alone and ADHD +emotion dysregulation	Treating 'core' ADHD benefits emotion dysregulation but separate treatment may also be needed