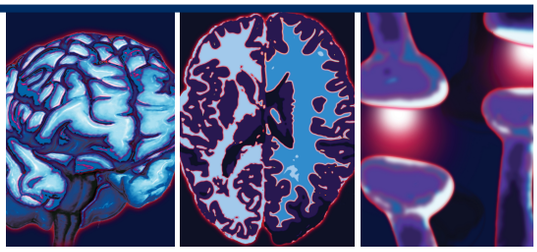
EDITORIAL



Testosterone, emotion regulation and childhood aggression

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"...we propose that disorders of childhood aggression are compounded by the effects of testosterone upon the emotion regulation system."

Childhood aggression is one of the most significant mental health problems that children and their families suffer. Simultaneously, disorders that include maladaptive aggression within their criteria, most notably oppositional defiant disorder (ODD), remain among the most poorly neurobiologically characterized disorders of psychiatry [1]. Whereas the neuropsychiatric basis of other childhood disorders, such as the autism spectrum disorders (ASDs) and ADHD, are now widely accepted, regrettably, it is still common to hear ODD labeled as a disorder of 'bad parenting' and managed through strictly behavioral approaches. Neuropsychiatry, as both a field and an endeavor, would be greatly advanced through further study of the neurobiological basis of childhood aggression.

Testosterone provides a promising conduit through which to proceed. Testosterone has long been associated with aggression in postpubertal adolescents and adults, and its neural signature on healthy brain functioning has been recently defined [2]. Testosterone levels have been linked in adults to unfortunate manifestations of aggression, including violent offenses and suicide [3]. Among other mechanisms, it appears that testosterone may inhibit effective self-regulative capacities. The abiltiy to regulate one's emotions is an important capacity that has been well defined within the field of affective neuroscience [4].

Emergent studies in children suggest that these findings may be equally applicable in school-age and even toddler populations, where differences between the sexes in the prevalence of physical aggression exist at as early as 17 months of age [5]. In building upon pre-existing neuropsychiatric models of childhood aggression [1], we propose that disorders of childhood aggression are compounded by the effects of testosterone upon the emotion regulation system.

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Testosterone, emotion regulation & early brain development

The development of the human brain and emotion regulation processes are intimately

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affected by testosterone [6]. These effects begin with a sexually dimorphic surge in fetal testosterone during weeks 8–24 of gestation. A second surge occurs in the first 3 months of life. These two events constitute the major testosterone-mediated organizational periods of brain development. Later, pubertal testosterone will directly exert activating effects upon this circuitry to further stimulate sex-characteristic behaviors.

We now know the neuroanatomical correlates of these organizational effects. Although prior studies failed to find any region-dependent effects of indirect measurements of fetal testosterone [7], a 2012 study by Lombardo now reveals that fetal testosterone levels correlated negatively with prefrontal gray matter volumes and positively with those of amygdala regions [8]. Given what we already know of the neural architecture of normative emotion regulation, this pattern of influence immediately suggests that testosterone may play a key role in self-regulative impairment, as well as in the normal physiology of emotions.

Emotion regulation and the full complement of its neuroanatomic correlates develops within the first 3–4 years of life [9]. Young neonates lack self-regulative capacities. Infants learn to reorient their attention away from distressing stimuli. Toddlers exert effortful control against responses to emotionally negative stimuli. This development is paralleled neuroanatomically from a shift in reliance from inferior and superior parietal areas, and the frontal eye fields towards a vertical system within medial brain structures. This system is essentially the same as that which is well defined in adults [4].

In this system, self-regulative processes may be divided into implicit and explicit processes [10]. Implicit regulation, or implicit environmental and self-evaluations with immediate response tendencies, is dependent upon the ventral prefrontal cortex (PFC), which includes the orbitofrontal cortex, ventromedial PFC and ventral anterior cingulate cortex. Explicit regulation, or deliberate or effortful conscious cognitive manipulations that monitor, adjust and select responses from a range of options, is dependent upon the dorsal anterior cingulate cortex and dorsolateral PFC. These two divisions of the cerebral cortex both modulate lower brain structures, including the amygdala, hypothalamus and brainstem nuclei, through their respective regulative pathways. The successful modulation of these visceromotor centers through the PFC regulators leads to increased vagal tone and decreased sympathetic arousal. This affects a measurable neurochemical state that promotes calmness and inhibits behavioral dysregulation.

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Aggression & affect

It appears that testosterone-mediated developmental inhibition of prefrontal areas impairs emotion regulation capacities in childhood, which may result in dysregulated aggression. A useful, if imperfect, emerging research heuristic by which to test this claim has been the division of aggression into reactive and proactive subtypes [11]. Whereas the latter has been described as calculated, callous and effected to achieve some personal gain, the former has been termed 'hot' aggression. Although these types of aggression likely exist on a continuum, the construction of the reactive aggression pole allows for the study of a homogenous and common form of childhood aggression [12].

The recent division of ODD criteria into 'irritable', 'headstrong' and 'hurtful' clusters [13] will be intergrated into the DSM-5 [14]. Study of the irritable cluster, as well as the new diagnosis of disruptive mood dysregulation disorder [14], will permit a greater understanding of reactive aggression. These criteria include 'is often touchy or easily annoyed', 'is often angry or resentful', and 'often loses temper.' By contrast, children prone to proactive aggression include those of the 'headstrong' cluster, which includes 'often deliberately annoys people', 'often actively defies or refuses to comply with adults' requests or rules', and 'often argues with adults'. Children with a predominance of the irritable criteria are more likely to go on to develop affective disorders, whereas those of the headstrong criteria are predisposed to conduct disorder and possibly antisocial personality disorder [13].

Despite the phenomenological disparity between these two major types of youth aggression, the male sex hormone, testosterone, may play an intimate role in the development and maintenance of each type of aggression. Although earlier findings were often contradictory and inconclusive, more recent studies seem to support a positive association between undifferentiated aggression and the organizational effects of testosterone in young children [15,16]. We have described how testosterone affects the emotion regulation pathways that are related to reactive aggression. Emerging electroencephalographic studies of aggressive preadolescents, which show correlates of functional disruption

in the PFCs, are now beginning to confirm this hypothesis [17,18].

Treatment implications & further research

A perspective that views childhood reactive aggression as the product of a deficit in the child's capacity to process painful affect offers an opportunity to complement the therapeutic successes of behavioral approaches to childhood aggressive behaviors. We may further this suggestion by considering that the specific area inhibited in preadolescents in the Lombardo study was the orbitofrontal PFC [8]. This suggests that implicit self-regulative processes may be particularly affected by testosterone. We know that this area of the PFC is particularly important to background feelings or emotional states that make up conscious experience but are not noticed as such unless they are attended to [19]. Males may, therefore, be at a particular disadvantage relative to their female peers to appropriately modulate backgrounded affective states.

One of us (Rice) is working to develop a manualized treatment approach to target these specific neurobiological deficits. This approach proceeds through an integrated dynamic and exposure-response prevention paradigm, in which youths are gradually exposed to painful background feelings. Dysregulated aggressive responses are prevented through gradual construction of intact emotional regulation capabilities. This approach directly addresses neurobiological deficits in lieu of descriptive, categorically-defined disorders. Children with ODD, in particular those with a predominance of symptoms within the irritable cluster, and disruptive mood dysregulation disorder will be treated with this approach.

An alternative cognitive-behavioral approach works to shift regulative processes from the reactive to the effortful. Utilized techniques include cognitive restructuring, problem-solving, role-playing and generalization activities. One preliminary study of self-regulation training in aggressive children found that normalization of electroencephalographic emotional regulation correlates among treatment responders [18]. Whether the development of alternative neuronal processes superimposed upon self-regulative deficiencies are equivalent to extinction process geared directly at maladaptive regulation remains to be tested. It is now important to consider that affect-oriented approaches to childhood aggression may provide treatment frameworks that share greater accord with emerging neuropsychiatric models of these disorders.

Understanding childhood reactive aggression as the result of a disturbance in the processing of painful affect offers new opportunities in both clinical practice and research. The study of testosterone has facilitated this understanding. There are correlates in many other neuropsychiatric disorders of childhood that manifest with reactive aggression and often comorbid ODD, including the ASDs, ADHD, Tourette's disorder and obsessive–compulsive disorder. Each of these disorders are more likely to be diagnosed in males than in females. Sex ratios range from approximately 3:1 (obsessive–compulsive disorder, ADHD and Tourette's disorder) to 5:1 (ASDs) in males compared with females. We may hypothesize that attention to the effects of testosterone upon the emotional regulation system, superimposed upon the disorder-specific neuroanatomical deficits of these diverse childhood disorders, may help us to understand a diverse array of childhood psychopathology; however, further studies are needed.

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