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Dysfunction in the Neural Circuitry of Emotion Regulation—A Possible Prelude to Violence

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Emotion is normally regulated in the human brain by a complex circuit consisting of the orbital frontal cortex, amygdala, anterior cingulate cortex, and several other interconnected regions. There are both genetic and environmental contributions to the structure and function of this circuitry. We posit that impulsive aggression and violence arise as a consequence of faulty emotion regulation. Indeed, the prefrontal cortex receives a major serotonergic projection, which is dysfunctional in individuals who show impulsive violence. Individuals vulnerable to faulty regulation of negative emotion are at risk for violence and aggression. Research on the neural circuitry of emotion regulation suggests new avenues of intervention for such at-risk populations.

The prevalence of violence in our society has stimulated both social and biological scientists to search for the predictors and causes of this often destructive human behavior. Here we focus on the nature of the affective style that might predispose an individual to this aberrant form of behavior. Affective style is a term that refers to consistent individual differences in the various parameters that govern emotional reactivity (*1*). We contend that the propensity for impulsive aggression is associated with a low threshold for activating negative affect (a mixture of emotions and moods that include anger, distress, and agitation) and with a failure to respond appropriately to the anticipated negative consequences of behaving aggressively.

Social psychological research underscores the relation between aggression and emotion. Numerous studies show that negative affect can precipitate and accentuate aggressive behavior (*2, 3*). In this article we feature those forms of aggression that are relatively unplanned and spontaneous, termed impulsive aggression (*4*), which is different from premeditated aggression (*5*). Although most neurobiological studies of aggression and violence typically do not differentiate between premeditated and impulsive aggression, this distinction is likely relevant in understanding their genetic, neurochemical, and functional neuroanatomical bases, and consequently, we have confined our discussion to impulsive aggression, which often culminates in physical violence.

Emotion Regulation: Core Neural Substrates

As reviewed recently (*6, 7*), a circuit that includes several regions of the prefrontal cortex (PFC), the amygdala, hippocampus, hypothalamus, anterior cingulate cortex (ACC) (*8*), insular cortex, ventral striatum, and other interconnected structures has been implicated in various aspects of emotion, affective style, and emotion regulation (Fig. 1). Emotion regulation includes processes that amplify, attenuate, or maintain an emotion. Here we will focus on the associated affective phenomena of anger, general negative affect, and impulsive aggression (*3*).

A variety of evidence indicates that the amygdala is crucial for learning to associate stimuli with primary punishers and rewards (i.e., those events that are intrinsically punishing or rewarding) (*10, 11*). In human neuroimaging studies, the amygdala is activated in response to cues that connote threat (such as facial signs of fear) (*12, 13*), as well as during induced fear (for example, fear conditioning) (*14, 15*) and generalized negative affect (for example, negative affect provoked by watching unpleasant pictures) (*16*). Patients with selective bilateral damage to the amgydala have a specific impairment in the recognition of fearful facial expressions (*17*). The amygdala is more strongly activated by facial expressions of fear than it is by other facial expressions, including anger. For example, increasing intensity of fearful facial expressions is associated with activation of the amygdala. In contrast, increasing intensity of angry facial expressions is associated with increased activation of the orbitofrontal cortex (OFC) and the ACC (*18*). In two neuroimaging studies that have attempted to induce anger specifically (*19, 20*), normal subjects showed increased activation in the OFC and ACC. These activations may normally be part of an automatic regulatory response that controls the intensity of expressed anger. We would expect that in individuals prone to aggression and violence, the increase in OFC and ACC activation usually observed in such conditions would be attenuated.

A large corpus of animal studies has examined the anatomical and neurochemical substrates of fear-potentiated startle reflexes in which modulation of the magnitude of the startle response by concomitant emotion is measured (*21*). This research is now being extended to humans to probe the chronometry and regulation of emotion (*22–26*).

The circuitry underlying this phenomenon has been well characterized in rodents and includes a descending pathway from the central nucleus of the amygdala to the nucleus pontine reticularis in the brain stem that serves as the proximal substrate of the reflex. In rodent studies, the accentuation of the startle response magnitude during fear is produced by the amygdala amplifying the brain stem startle circuit. Lesions of the central nucleus of the amygdala have no effect on baseline startle, but they abolish the fear-potentiation of the startle response (*27*).

In analogous studies in humans, when subjects view unpleasant pictures, there is an increase in the magnitude of the eyeblink reflex (measured from surface electromyographic recording from the orbicularis oculi muscle) in response to a brief burst of noise (*28*). Moreover, the magnitude of the eyeblink reflex to the same stimulus during the viewing of pleasant pictures is smaller than that during the viewing of neutral pictures (*28, 29*).

By triggering a startle response at different times during affective processing, information about the time course of emotion can be gleaned (*23–25, 30*). In one experiment (*25*), normal subjects viewed unpleasant or neutral pictures for 8 s. Four seconds after the picture appeared, a digitized human voice instructed the subject to regulate the emotion they were experiencing in response to the picture. For unpleasant pictures, subjects were asked to suppress, enhance, or maintain their emotional response. Subjects were instructed to continue voluntary regulation of their emotional response even after the picture disappeared. During and after the presentation of the pictures, brief noise bursts were presented to probe the time course of the emotion before and after the instruction to regulate was presented. When subjects were requested to suppress their negative

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affect, they showed significantly diminished startle magnitude during and after unpleasant pictures compared with both the maintain and enhance conditions (Fig. 2). Most important was the fact that subjects varied considerably in their skill at suppressing negative emotion. By inserting startle stimuli before the instruction was presented, we confirmed that this variation in the ability to regulate emotions could not be accounted for by differences in the initial reactivity to the negative stimuli. In more recent work (*26*), we found that baseline levels of regional brain activation inferred from high-density scalp-recorded brain electroencephalography (EEG) (*31*) predicted the ability of subjects to suppress emotions. Those subjects with greater relative left-sided activation in prefrontal scalp regions showed greater startle attenuation in response to the suppression instruction. Although the EEG methods used in this study precluded definitive localization of the sources of these signals, other evidence implicates the OFC in this process. Research with humans who have selective damage to the OFC or ventromedial PFC (*32*), and with nonhuman primates, supports the role of these prefrontal territories in reversal learning [changing emotional behavior in response to a previously rewarded or punished stimulus (*10*)]. Suppressing negative affect in response to a stimulus that previously aroused such emotion can be conceptualized as a form of reversal learning. Patients with lesions in the OFC and those vulnerable to impulsive aggression should be particularly deficient in this task, although they would still show the basic enhancement of startle magnitude in response to negative stimuli.

We have proposed that the mechanism underlying suppression of negative emotion is via an inhibitory connection from regions of the prefrontal cortex, probably the OFC, to the amygdala (*7*). This proposal is based on several lines of evidence. First, data in rodents show that lesions of the PFC interfere with extinction of a classically conditioned aversive response [(*33*), but see (*34*)], implying that the PFC normally inhibits the amygdala and that, when the PFC is lesioned, it releases the amygdala from this inhibition and results in much slower extinction of aversive responses. Second, data from a positron emission tomography (PET) study show reciprocal relations between glucose metabolism in several areas of the frontal cortex (including the OFC) and the amygdala (*35*).

On the basis of this reasoning, we examined by functional magnetic resonance imaging (fMRI) amygdala activation after subjects were instructed to maintain a negative emotion as compared with the subjects' simple passive viewing of unpleasant pictures. We found greater activation of the amygdala after the picture was turned off in the group asked to maintain that emotion as compared with the "passive viewing" condition, as the model would predict (*36*).

The implications of these findings are several: First, individual differences in the capacity to regulate emotion are objectively measurable. Second, individual differences in patterns of prefrontal activation predict ability to perform this task and thus reflect differences in aspects of emotion regulation. Third, individual differences in emotion regulation skills, particularly as they apply to suppression of negative affect, may be especially important in determining vulnerability to aggression and violence.

The Neurobiology of Anger and Aggression

Disruption of the serotonin (5-HT) system has been linked to aggression and violence by a variety of methods. Serotonin has been hypothesized to exert inhibitory control over impulsive aggression (*37*). Cerebrospinal fluid (CSF) level of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) is believed to reflect presynaptic serotonergic activity in the brain. Reduced CSF 5-HIAA has been found in aggressive psychiatric patients (*38, 39*); impulsive, violent men (*40, 41*); and victims of suicide by violent means (*42*). Furthermore, 5-HIAA concentration has been found to predict aggression 2 to 3 years in the future in conduct-disordered boys (*43*) and recidivous adults (*44*). Lower CSF 5-HIAA levels have been reported in impulsive violent offenders (*45*) and impulsive fire setters (*46*) than in nonimpulsive violent offenders.

Pharmacological challenge studies provide another indirect method for studying central serotonin function. The prolactin elevation in response to a single dose of a 5-HT agonist has been used to index central 5-HT activity. Lower prolactin responses to a 5-HT agonist have been associated with aggressivity (*38*), antisocial personality disorder (*47*), and suicidal behavior (*38*). Traits of aggression in a large normative community-derived sample were associated with lower prolactin responses to the 5-HT agonist fenfluramine in men (*48*). The synthesis of 5-HT depends on the availability of the amino acid tryptophan. By limiting dietary tryptophan, brain levels of 5-HT can be reduced (*49*). Tryptophan depletion induced by consuming a beverage containing a group of amino acids without tryptophan increased laboratory aggression in normal men (*50, 51*) and both spontaneous and competitive aggression in monkeys (*52*), as compared with increasing tryptophan with

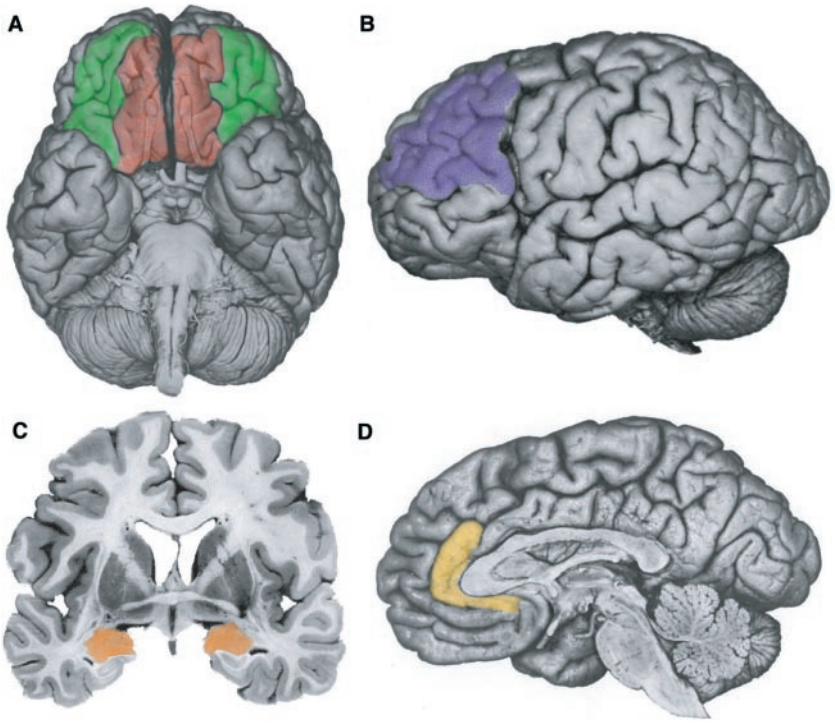

Fig. 1. Key structures in the circuitry underlying emotion regulation. (**A**) Orbital prefrontal cortex in green and the ventromedial prefrontal cortex in red. (**B**) Dorsolateral prefrontal cortex. (**C**) Amygdala. (**D**) Anterior cingulate cortex. Each of these interconnected structures plays a role in different aspects of emotion regulation, and abnormalities in one or more of these regions and/or in the interconnections among them are associated with failures of emotion regulation and also increased propensity for impulsive aggression and violence. [Adapted from (*9*)]

a tryptophan-containing beverage.

A polymorphism in the gene that codes for tryptophan hydroxylase (TPH), the rate-limiting enzyme in serotonin biosynthesis, is correlated with indirect measures of central serotonergic function, as well as individual differences in aggressive behavior (*53, 54*). In a study (*54*) with 251 community volunteers, the association between the A218C polymorphism in intron 7 of the TPH gene and interview and self-report measures of aggression and anger-related personality traits was examined. In addition, a fenfluramine challenge was administered to a subsample. Subjects having any TPH A218C U allele scored significantly higher on several measures of aggression, including the tendency to experience unprovoked anger, than individuals homozygous for the alternate A218C L allele. Among the male subjects, prolactin response to fenfluramine was also blunted in those subjects having any U allele compared with the LL homozygotes.

The PFC, an important component of a circuit critical to emotion regulation that has been implicated in aggressive and violent behavior, is a region with a high density of serotonin type 2 receptors (*55*). In a study designed to evaluate the functional impact of a serotonergic challenge on regional cerebral glucose metabolism, Mann and his colleagues (*56*) administered either fenfluramine or a placebo to normal subjects on two separate occasions while cerebral glucose metabolism was measured with PET. Significant drug-induced increases in glucose metabolic rate were found in left hemisphere regions of the PFC, including the inferior and middle frontal gyrus, ventromedial PFC, and anterior cingulate. These regions include those with activation inversely associated with activation in the amygdala (*35*).

The increase in glucose metabolism in PFC and ACC regions in normal subjects in response to fenfluramine is blunted or entirely absent in patients with aggressive impulsive personality disorder (*57, 58*). These findings imply that an important site of serotonergic abnormality in subjects with impulsive aggression is the prefrontal cortex, which likely plays a role in emotion regulation, particularly the regulation of negative affect.

Studies of regional glucose metabolism assessed with PET (unprovoked by pharmacological challenge) also reveal prefrontal abnormalities in individuals prone to impulsive aggression (*59–63*). A study of 41 murderers (*62*) found hypoactivation in prefrontal territories including lateral and medial zones of the PFC, as well as hyperactivation in the right but not the left amygdala, compared with age- and sex-matched controls. In a subsequent reanalysis of these data (*63*), murderers were classified as those who committed planned, predatory murder or those who committed affective and impulsive murder. The affective, impulsive murderers showed reductions in lateral PFC metabolism compared with controls, whereas the predatory group did not. Subcortical regions were averaged together in this report and included the hippocampus, amygdala, thalamus, and midbrain. An increased metabolic rate was observed in these regions in the right hemisphere in the affective, impulsive murderers as compared with the other groups.

Lesions in the OFC and adjacent PFC regions produce syndromes characterized by impulsivity and aggression. Anderson *et al.* (*64*) reported on two individuals, tested in their twenties, who suffered early damage (ages 3 and 15 months) to orbital and lateral sectors of the PFC. Both exhibited a remarkable deficit in moral reasoning; a history of verbal and physical abusiveness; and intermittent, explosive bursts of anger. Blair and Cipolotti (*65*) reported that a 56-year-old man (J.S.), who sustained damage to the OFC bilaterally and some damage to the left amygdala, showed unpredictable, impulsive aggression and violence. J.S. was described by a relative "as being premorbidly a quiet, rather withdrawn person who was never aggressive" (p. 1124). In a series of tasks administered to J.S., a control patient with damage to other sectors of the PFC, and a small group of psychopathic and nonpsychopathic individuals, J.S.'s pattern of affective processing abnormalities was identified. He had deficits in recognition of facial expression, and he was particularly impaired relative to all other groups in the recognition of anger and disgust. J.S. also produced significantly lower skin conductance responses to the anger and disgust expressions compared with the comparison groups. In response to threatening objects such as pointed weapons, J.S. was hyporesponsive compared with other groups. Thus, J.S. exhibited a strikingly specific deficit in the recognition of anger signals and in inferring the emotions of others in situations where anger, disgust, and embarrassment are usual. Facial and other expressive signs of anger function to inhibit the behavior of others in situations where social rules or expectations may be violated.

In other related work, patients with antisocial personality disorder who exhibit a propensity for impulsive aggression exhibit an 11% reduction of overall prefrontal gray matter volume by MRI (*66*). Interictal episodes of impulsive aggression are sometimes observed in patients with temporal lobe epilepsy (TLE). TLE patients who display such episodes of impulsive aggressive (diagnosed as having intermittent explosive disorder) have a highly significant reduction (approximately 17%) in left prefrontal gray matter as compared with TLE patients with no history of aggression or controls (*67*).

Emotion Regulation, Aggression, and Violence: Common Neural Substrates?

Impulsive, affective aggression may be the product of a failure of emotion regulation. Normal individuals are able to voluntarily regulate their negative affect and can also profit from restraint-producing cues in their environment, such as facial and vocal signs of anger or fear, that also serve a regulatory role. We suggest that individuals predisposed to

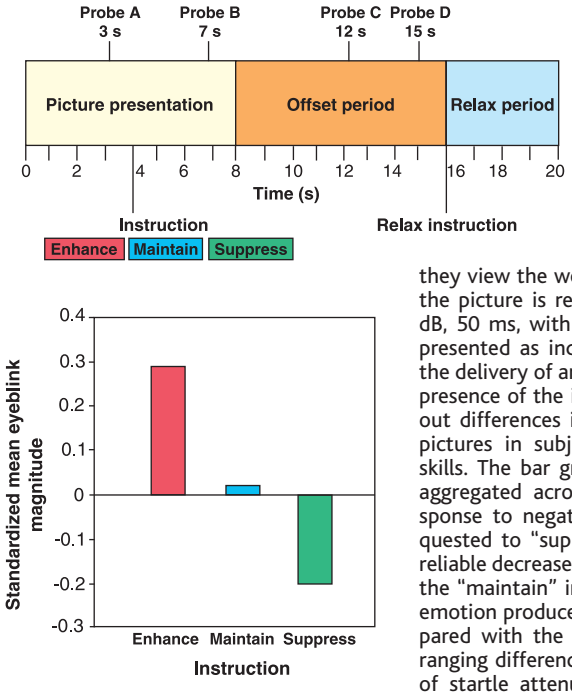

Fig. 2. Experimental paradigm for investigating emotion regulation (*25*). Unpleasant or neutral pictures are presented during the 8-s picture presentation period illustrated in yellow. At 4 s into the picture presentation, an instruction (ENHANCE, MAINTAIN, OR SUPPRESS) is presented. Subjects are instructed to continue to execute the regulatory strategy until they view the word RELAX that is presented 8 s after the picture is removed from sight. Noise bursts (95 dB, 50 ms, with a near instantaneous rise time) are presented as indicated. Probe A is presented before the delivery of any regulation instruction to verify the presence of the intended emotional state and to rule out differences in initial reactivity to the emotional pictures in subjects who differ in their regulatory skills. The bar graph displays data from 43 subjects aggregated across all postinstruction probes in response to negative pictures. When subjects are requested to "suppress" negative emotion, they show reliable decreases in startle magnitude compared with the "maintain" instruction. Instructions to "enhance" emotion produce increases in startle magnitude compared with the other conditions. There were wide-ranging differences among subjects in the magnitude of startle attenuation in response to the SUPRESS instruction.

aggression and violence have an abnormality in the central circuitry responsible for these adaptive behavioral strategies. Four key regions that are components of a circuit underlying emotion regulation are illustrated in Fig. 1. Functional or structural abnormalities in one or more of these regions or in the interconnections among them can increase the propensity for impulsive aggression. The evidence reviewed above suggests that abnormalities in serotonin function in regions of the PFC may be especially important. Other neurotransmitters, neuromodulators, and hormones are also likely involved, including testosterone (*68*), norepinepherine, dopamine and cortiocotropin-releasing hormone (*42*), and cholesterol (*69*), although none of these has received much attention in human studies of aggression and violence.

The role of the amygdala in impulsive aggression is complex (*70*). Individual behaviors that connote threat (e.g., staring eyes, threatening vocalization, lunging posture) are conveyed to the lateral nucleus of the amygdala, which then projects to the basal nuclei, and it is there that information about the social context derived from OFC projections is integrated with the perceptual information (*71, 72*). Behavioral responses can then be initiated via projections from the basal nuclei to various cortical zones, and physiological responses can be produced via projections from the basal nuclei to the central nucleus and then to the hypothalamus and brainstem. Too much or too little activation of the amygdala may give rise to either excessive negative affect or decreased sensitivity to social cues that regulate emotion, respectively.

The evidence we have reviewed indicates that the OFC and the structures with which it is interconnected (including other prefrontal territories, the ACC, and the amygdala) constitute the core elements of a circuit that underlies emotion regulation (Fig. 1). The OFC, through its connections with other zones of the PFC and with the amygdala, plays a crucial role in constraining impulsive outbursts, and the ACC recruits other neural systems, including the PFC, in response to conflict (*8*). In normal individuals, activations in these brain regions that occur during anger arousal and other negative emotions constrain the impulsive expression of emotional behavior. Deficits in this circuit are hypothesized to increase a person's vulnerability to impulsive aggression.

There are many factors that influence the structure and function of this circuitry. Genetic factors clearly play a role as revealed by the association of the polymorphism of the TPH gene with traits of anger and aggressivity (*54*). However, these factors undoubtedly interact with early environmental influences (*73*). Moreover, the very circuitry identified here as playing a crucial role in emotion regulation is dramatically shaped by early social influences (*7*). Interventions that combine pharmacological (*74*) and psychosocial strategies will likely both operate on a common final pathway in the emotion regulatory circuitry of the brain. Novel training procedures based upon experimental paradigms now being used to study the neural substrates of emotion regulation (e.g., suppressing negative emotion) need to be developed and then rigorously evaluated. Nevertheless, the first important step is to recognize that impulsive aggression and violence, irrespective of the distal cause, reflect abnormalities in the emotion regulation circuitry of the brain.

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