The Dialectic Between Empathy and Violence: An Opportunity for Intervention?

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The authors provide a comprehensive review of the neurobiology of empathy and compare this with the neurobiology of psychopathic predatory violence—the most extreme deficit of empathy. This suggests that the specific areas of the prefrontal cortex and limbic system, which have been associated with violent behavior, also appear to subserve the capacity for empathy. Damage to these regions may result in the emergence of aggression, but not of empathy, suggesting a structurally inverse relationship between the two. The authors examine the evidence for a dialectic between empathy and predatory violence and explore the implications for early interventions with empathy training in treatment-resistant psychopathy.

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The search for a violence center within the brain has preoccupied anatomists and behaviorists for centuries. In the recent past, deficits in specific areas of the prefrontal cortex (PFC) and the limbic system have been most consistently associated with violent behavior.[1] Similar regions of the brain also subserve the capacity for empathy. Damage to these regions may result in the emergence of aggression but not empathy, suggesting an inverse relationship between empathy and violence. This review of the neurobiology of empathy compared with the extreme deficit of empathy (i.e., psychopathic predatory violence [PV]) points to the possibility that early interventions with empathy training may lessen psychopathy resistance to treatment.

DEFINING EMPATHY

Empathy, or "feeling as another does,"[2] functionally comprises four dimensions. Empathy is (a) an affective state that is (b) isomorphic to another person's affective state, (c) is elicited by observing or imagining another person's affective state, and (d) is experienced while remaining cognizant that the other person's affective state is the source of one's own affective state.[3,4] The development of empathy is preceded by, and emerges from, more elementary functions such as brainstem-mediated mimicry, which is present at birth, and mirror-neuron–mediated emotional resonance, which emerges in the very first months of life.[5] Both of these functions induce physiological changes, such as facial grimacing or pupillary dilation, in response to the expressions, vocalizations, postures, and movements of another person.[6] During the second year of life, at the same time as frontally mediated self/other cognitive awareness begins to develop, this capacity to send and respond to limbic-modulated emotional signals evolves into more mature forms of empathy. Our capacity to distinguish whether the source of an affective experience is triggered by another or lies within ourselves is a key characteristic of empathy[7] and is part of a broader capacity for perspective taking. Although compassion (i.e., sympathy or empathic concern) also induces affective changes in the observer, empathy denotes that the observer's emotions reflect affective sharing ("feeling as" the other person), whereas compassion denotes that the observer's emotions are inherently other oriented ("feeling for" the other person).[8] Empathic perspective taking also partially differs from mentalizing and theory-of-mind functions, which involve taking another person's perspective and attributing to them particular cognitive states, in that it is more involved in attributing emotional states.[9]

THE NEUROBIOLOGY OF EMPATHY

The PFC is subdivided into five frontal-subcortical regions, two of which have most consistently been implicated in violent and empathic behavior: the dorsolateral prefrontal circuit, which connects pathways that modulate executive functions, including the ability to plan, problem solve, sequence events, and adaptively change cognitive and behavioral sets; and the orbitofrontal circuit, which connects frontal monitoring pathways to the limbic system and governs appropriate responses to social cues and interpersonal sensitivity.[10] Corticolimbic networks subserving distinct social functions can be further divided into three partially

dissociable networks: perceptual, subserving awareness/understanding of others' socioemotional behavior (lateral orbitofrontal cortex [OFC], ventrolateral temporal pole, fusiform gyrus, superior temporal sulcus); reward/affiliation, subserving socioemotional responsiveness/detachment (dorsomedial temporal pole, rostral anterior cingulate cortex, subgenual anterior cingulate cortex, ventromedial PFC [vmPFC], entorhinal cortex, parahippocampal cortex, ventromedial striatum); and pain/aversion, subserving threat detection and approach-avoidance behaviors (caudal anterior cingulate cortex, insula, somatosensory operculum, ventrolateral striatum).[11] The limbic system includes the amygdala, which attributes emotional valence to memories; the hypothalamus, which receives information about the internal state of the body and orchestrates endocrine/hormonal responses through its control of the pituitary gland; and the cingulate gyrus, which is involved in autonomic regulatory functions such as heart rate and blood pressure.[1]

The affective and cognitive components of empathy are dissociable, as indicated by neurological[12,13] and functional[14,15] studies as well as by their different developmental trajectories.[16,17] Mature empathic sensitivity depends on the functional integration of these components, expressed via emotional regulation and attachment behaviors, which typically develop in tandem.

The affective component of empathy relies on a neural resonance system by which an observer engages motor intention,[18] sensory experience,[19] and visceral state[20] neural mechanisms, which overlap with those that the individual would engage if he or she were directly experiencing a given internal state. The cognitive component of empathy engages the ability to represent affective states outside of a perceiver's present experience to include anticipated experiences or the experiences of another (self-projection).[21,22] Brain regions most typically associated with affective empathy include the inferior parietal lobule, anterior insula, posterior superior temporal sulcus, and anterior cingulate cortex. Cognitive empathy engages a system of midline and superior temporal structures broadly involved in "self-projection" and mentalizing. These include the temporoparietal junction, temporal poles, medial PFC, posterior cingulate cortex, and precuneus.[4]

Although these brain regions that subserve affective and cognitive components constitute a complex distributed and recursively interconnected network, further activating autonomic and neuroendocrine processes implicated in social behaviors and emotional states,[8] recent studies have begun to detect temporal dynamics within the process of empathic experience that indicate brain activity associated with affective sharing comes online earlier than the mentalizing-related activity.[23]

Developmental shifts take place within this network, which allow for the transition from emotional arousal and self-distress to more mature empathic responsiveness.[24] As a child matures from 6 to 11 years old, the self/other awareness circuit becomes more selectively responsive to perspective-taking situations that require inferring the mental states of others.[25] At the same time, the development of affective processing from childhood to adulthood is accompanied by reduced activity within the brainstem and limbic affective systems and by the increased involvement of the PFC.[26] In response to others' distress, younger children recruit the amygdala, medial OFC, and posterior portion of the insula more so than adults.[27] As children mature, the activity of the medial OFC, which is involved in regulating motor and visceral responses, decreases and the activity of the lateral OFC, which is involved in executive control of emotion reactivity, increases.[28] This pattern of developmental change is indicative of a gradual shift from the monitoring of somatovisceral responses in young children to a more cognitive, evaluative level, which is associated with executive control of emotions in adults.[29] As cortical executive functions mature through childhood and adolescence, inhibitory capacities and attentional control strengthen, allowing for more fine-tuned emotional regulation. Activation of these prefrontal functions reduces amygdala and autonomic reactivity.[30] Overall, as children mature, there is a progressive shift from more limbic to more frontal activation. Inhibitory control and emotional regulation are linked to the ventral and dorsal aspects of the PFC and to the dorsal anterior cingulate cortex, both through their reciprocal connections with limbic areas.[31] Emotional regulation is fundamental for the capacity to experience empathy rather than personal distress.[27] Well-regulated children are more prone to empathy, regardless of their emotional reactivity, because they have learned, in part through the support of their caregivers, to modulate their negative vicarious emotions to maintain an optimal level of emotional arousal. By contrast, children who are unable to regulate their emotions tend to be low in empathy and to become overwhelmed by their negative emotions when witnessing another in distress.[16]

Empathy evolves in the service of attachment for self-preservation. Empathy enhances survival by bonding individuals, especially mother and infant, thereby increasing defenses against predators.[32] By reducing personal distress and avoidance behaviors, secure attachment facilitates affect regulation, in turn increasing empathic behaviors.[16] Children with secure attachment are more empathic toward others, regardless of relatedness.[33] Conversely, lack of secure attachment increases avoidant behavior, emotional distress, and lack of empathy.[34] The degree of empathic responsiveness directly correlates with approach-avoidance behaviors, which directly modulate attachment. Approach-avoidance behaviors are hormonally modulated.[35] In humans, the hypothalamus-pituitary-adrenal (HPA) axis and oxytocin are particularly relevant. The HPA axis is functional at birth and matures rapidly during the early years, lessening emotional lability and increasing self-control.[36] This process is strictly linked to the presence and responsiveness of an attachment figure in the child's life, which specifically triggers up/down HPA regulation,[37]

with gender- and parental-status differences in neurohemodynamic brain responses to infants. Female, but not male, individuals exhibit regulatory changes in response to infant stimuli, with mothers showing greater modulation in response to crying and nonmothers in response to laughing.[38] The social modulation of physiological stress responses continues to influence HPA activity in adults and provides a buffer against stress.[39] The extent of this shift is also affected by individual predisposition toward autonomic arousal, emotional reactivity, and strength of executive functions. Oxytocin, which is released in the context of supportive relationships, has specific modulatory effects on the HPA axis. By downregulating the HPA axis, it induces increased tolerance to stressful stimuli by reducing pain sensitivity, fear/anxiety, and defensive avoidance, thereby enabling greater trust, attachment, and empathy.[40] Both secure attachment and higher degrees of empathic capacity hormonally activate the brain reward system, which, in turn, sustains attachment and nurturance. Because empathy and attachment are linked to the same hormonal events, they are both behaviorally and physiologically interdependent. The hormonal shifts of pregnancy predispose the brain reward system to form mother-infant bonds at birth,[41] while securely attached mother-child interactions increase the production of oxytocin, activating the brain reward regions.[42] Even when empathic behaviors are extended to nonkin, these behaviors activate the reward system, inducing feelings of well-being.[43] Thus, empathic behaviors are physiologically rewarding, if not addictive.[44]

AGGRESSION, VIOLENCE, AND THE LACK OF EMPATHY

Aggression is "an intentional act that inflicts bodily or mental harm on others,"[45] which is legitimate in certain contexts (e.g., self-defense) and may occur without bodily damage (e.g., verbal aggression). By contrast, violence is "an aggressive act that causes physical injury" and is the subset of aggression "characterized by the unwarranted infliction of physical harm."[45(p. 2)] This review focuses on interpersonal violence, excluding socially sanctioned types of violence (e.g., sports), warfare, totalitarian regimes, and organized crime (e.g., gangs, terrorism, and the Mafia). The literature on interpersonal violence distinguishes two main types of violence: impulsive violence (IV; "expressive," "affective," or "reactive"), which is characterized by rage or other intense emotions, and predatory violence (PV; "calculated/instrumental," "callous-unemotional" [CU], or "proactive").[46,47] Perpetrators who exhibit IV tend to target individuals with whom they have a connection: spouses, family members, coworkers, and schoolmates. Individuals who exhibit PV may target proximity victims, but they more often perpetrate PV against unknown others. We will make reference to IV only to the extent that it speaks to the understanding of PV. Although overt sexual violence is more present in IV, sexual arousal without overt sexual behavior is thought to be more present in PV, possibly as a motivating factor for the violent act. Acts without direct sexual contact may be arousing or otherwise intensely stimulating to the perpetrator. However, in the absence of scientific methods or criteria to distinguish impulsive versus predatory sexual violence, we will not consider the potential role of sexual violence in PV in this review.

PV may closely represent the inverse of empathy. Cold-blooded, purposeful PV is the hallmark of psychopathy.[48–50] Although they are not equivalent concepts, there is a substantial overlap between psychopathy and PV. Although not all psychopathic domains include opportunism and instrumentalism,[51] the literature on psychopathy consistently identifies both empathic deficits and predatory behaviors as the core signature of a psychopathic personality.[52] PV has also been found to correlate with an individual's total score on the Hare Psychopathy Checklist–Youth Version and interpersonal features of psychopathy.[50] The psychopathic behavior of PV is found in individuals who present with a dysfunction in either experiencing or sharing feelings with others, which is associated with deficits in affective empathy.[53,54] By contrast, individuals who exhibit IV tend to display disinhibition and intense emotions and more typically retain a capacity for empathy and remorse.[55] Unfortunately, the systematic investigation of psychopathy has been pursued only very recently, notwithstanding the descriptive reports of behavioral presentations such as the numerous editions of Cleckley's[56] *Mask of Sanity*.

THE NEUROBIOLOGY OF PV

Lesion and Genetic Correlates of PV

Lesion and brain-imaging studies have indicated that functional disruption of the PFC and limbic system (and with it, the HPA axis) can lead to the emergence of aggression and violence in a multitude of different conditions. However, lesion studies have failed to identify a specific violence center and have elicited a host of seemingly contradictory findings. Damage to the PFC can induce psychopathic traits such as lack of empathy and blunted emotions,[57] impaired moral judgment,[58] and impaired perspective taking with increased egocentrism and rigidity[10,59]; however, damage to the PFC more frequently induces emotional dysregulation, impulsivity, and poor planning.[57,60] Damage to the amygdala and hippocampus can induce increased avoidance behaviors[61] but can also increase startle reflex[62] and fear response.[63] Although these seemingly contradictory results are attributable to a range of anatomical and technological limitations intrinsic to lesion studies, which do not allow for fine neurobehavioral distinctions, it is an empirical fact that patients with acquired lesions in the vmPFC, OFC, and amygdalae and related limbic structures do not typically exhibit PV, although they may exhibit other forms of violence.[64] One reason for this is that these individuals may retain other functions that allow them to reflect and follow remembered rules, or they may retain important components

of empathy. The link between empathy and PV is not linear (all or none). Rather, the main structures and networks thought to participate in the dialectic between empathy and PV function in synchrony with and are finely modulated by input from other structures, often in recursive manners. Indeed, even some individuals with psychopathic behavior may express empathy for selected groups or animals or in specific situations.[65,66]

Genetic studies have suggested a predisposition to violence and aggression. Sibling and twin studies first provided evidence of familial aggregation of criminal activity and suggested that genetic factors account for approximately 40%−50% of the variance in transmission.[67] Genetic studies have supported a genetic predisposition only when including a broad range of antisocial behaviors[68] but have failed to provide evidence for a specific violence gene. The XYY chromosome theory, once linked to gender differences in violence, was not supported by further findings.[45] Although individual differences in monoamine oxidase-A (MAO-A) genetic alleles were once regarded as promising arenas for identifying a violence gene, studies have indicated that different versions of the gene are found in different individuals, that the distribution of these different versions differs from one ethnic group to another (making cultural-ethnic factors difficult to control),[69] and that MAO-A alleles have been associated only with broadly defined antisocial behaviors. An interaction between a history of childhood maltreatment and MAO-A status has been supported in some studies,[70] and other genes (catechol-*O*-methyltransferase, dopamine transporter 1, dopamine receptor genes DRD2 and DRD4, and serotonin transporter polymorphism) are being investigated as potentially linked to antisocial behavior.[71] Although multiple genes may interact to predispose individuals to violent behavior, the overall heritability rate of approximately 50% is similar to that for many other behaviors, indicating an equally important role of environmental factors.[72] Subsequent longitudinal studies of combined low-activity–inducing MAO-A variations and exposure to early traumatic life events have shown a correlation only with broadly defined antisocial behaviors.[70,73,74] There are also other problems with the view that MAO-A variations have a significant role in PV. Regardless of the allele type, significant levels of antisocial behaviors have been found in adults having no history of abuse.[70] Furthermore, the assumption that the level of allele activity directly affects the brain[70] has not turned out to be true in vivo, undercutting the view that the low-activity variant of the "warrior gene" actually results in low enzyme activity in the brain.[75] Finally, more than one in three men carry the relevant genetic variant, although the vast majority of them do not commit violent crimes. Thus, at most, this variant may produce a small increase in the risk for antisocial behavior among men with a history of abuse.[76] These studies indicate that violence is a multifactorial phenomenon, better understood within a framework of gene-environment interactions, with genetic differences creating a susceptibility to particular environmental risk factors. This paradigm can indicate a trend within a particular population but cannot make specific predictions at the individual level, where factors other than genetics play an equally important role. These studies also have not addressed the important distinction between IV and PV. The systematic investigation of PV has only been possible in recent years with the emergence of sophisticated neuroimaging technologies.

Structural and Functional Correlates of PV

The systematic investigation of the neurobiology of PV psychopathy was recently spearheaded by British neuroscientist Adrian Raine and his colleagues through a series of seminal articles, which indicate cognitive- and affective/emotional processing deficits in psychopathy associated with abnormal brain structure and function, particularly in the amygdala, OFC, and vmPFC, as well as possibly diminished cortisol levels.[46] Early brain-imaging studies were based on the broad clinical diagnosis of antisocial personality disorder,[48,77] without distinguishing between IV and PV. Because psychopathy was considered a subtype of antisocial behavior, these early studies failed to identify differences in their underlying deficits.[55,78,79]

In recent studies, PV was found to correlate with normal or increased prefrontal activity, increased intrafrontal connectivity, and reduced PFC-limbic/paralimbic functional connectivity, associated with inflexible behavior in PV psychopathy.[80–82] PV was also shown to correlate with hypometabolism in limbic structures (amygdala/hippocampal formation, parahippocampal gyrus, ventral striatum, and anterior/posterior cingulate gyri),[46,83] which correlates with shallow affect and lack of affective empathy; and, less frequently, hypermetabolism,[82] which is associated with aggressive impulses. Additional findings include volumetric changes, with increased callosal white matter volume and length, and increased functional interhemispheric connectivity, correlating mainly with deficient affect,[84] and deficits in the OFC, vmPFC, and cingulate cortex associated with impaired moral judgment. Conversely, IV has been found to relatively consistently correlate with PFC metabolic reduction, limbic hyperactivity, and lower prefrontal/subcortical ratios, indicating deficits in frontal regulation of limbic/paralimbic aggressive impulses.[82,85] Consistently, individuals with psychopathy have been found to suffer from emotional empathy deficit disorder (the capacity to experience or share emotions) subserved by the limbic system[17,86] but have retained the capacity to understand the feelings of others (cognitive empathy) subserved by the frontal circuits.[87,88]

Additional studies, without differentiating PV and IV, found decreased regional gray matter volume in the limbic/paralimbic regions, including the OFC, bilateral temporal poles, and posterior cingulate cortex,[89–91] and lower amygdala volume associated with higher levels of aggression and psychopathic features from childhood to adulthood.[92,93] Structural abnormalities have been found in psychopathic individuals with criminal convictions (termed "unsuccessful") relative to those without convictions (termed "successful").

Unsuccessful psychopathic individuals show increased anterior hippocampal volume asymmetry (right greater than left)[94] and reduced PFC gray matter volume.[95] These findings have been interpreted as correlating with emotional dysregulation and reduced fear conditioning in unsuccessful psychopathic individuals, who are consequently less sensitive to environmental cues of danger and capture. The significance of these findings will depend on whether they can be shown to consistently correlate with specific aspects of cognitive or affective processing in individuals who exhibit specific types of violence.

Neurochemical and Hormonal Correlates of PV

Motivated by the hope for neuropharmacological interventions, the neurochemistry of violence has received considerable attention. Testosterone has received particular attention, because the incidence of violence is much higher in male individuals and because involvement in crime usually rises in the early to mid-teens (when testosterone levels rise). A testosterone-aggression link has been shown in animal studies but has not been shown convincingly in humans.[96] For example, although incarcerated violent criminals have higher testosterone levels,[97] elevated testosterone levels may be an effect of violence, rather than a cause. It has been hypothesized that features of psychopathy such as hyporesponsivity to stressors, reduced fear, reduced sensitivity to punishment, and enhanced sensitivity to reward may result from the combined effect of reduced cortisol levels and increased testosterone levels.[98,99] The interplay between altered hormonal peripheral steroid hormones such as cortisol and the insula, anterior cingulate cortex, and amygdala has been found to be associated with diminished sensitivity to stress and increased callousness.[100] One study found that testosterone administration led to decreased sensitivity to punishment and increased sensitivity to reward.[101,102] These findings suggest a link between cortisol-testosterone balance and callousness, potentially predisposing to psychopathy.[103] Although neurotransmitters have been extensively investigated, studies suggest a link between serotonin and norepinephrine with impulsivity and with IV but not PV.[104] In addition, despite a growing literature on the dopaminergic and vasopressinergic systems,[99] little is known about the functional interaction of neurotransmitters with frontal and other neuroanatomical structures.[104]

Neuropsychological Deficits in PV

Although neuropsychological deficits in attention, language, and executive functioning have been found in the population who exhibits PV, their specificity is questionable. Disturbances of attention and executive functioning are present in many neurological disorders, both neurodevelopmental and acquired. Thus, these neuropsychological abnormalities may not be pathognomic of psychopathy. There is inconsistent evidence of superior capacity for selective or focused attention paired with diminished capacity for attention shifting to secondary information while engaged in goal-directed behavior (response modulation)[105] and of reduced capacity for divided attention (multitasking).[106] Investigations of complex executive functions have identified deficits in orbitofrontal-mediated speeded binary decision making (as assessed by the go/no-go test) and resistance to interference (as assessed by the Stroop test), but not in dorsolateral-mediated skills in set shifting, flexibility, and responsiveness to feedback (as assessed by the Wisconsin Card Sorting Test or the Trail Making Tests).[107,108] Orbitofrontal-mediated risk-taking tasks (e.g., the Iowa gambling task) have demonstrated consistent deficits,[109] although group differences secondary to reduced anxiety[110] or poor attention,[111] rather than psychopathy, could not be ruled out. Because psychopathic individuals typically express, in language, emotions that they do not feel, language processing has also been investigated. Studies have found a lack of facilitation on lexical-decision tasks for affective, relative to neutral, words[112]; significantly reduced affective, but not semantic, priming[107]; and reduced understanding of the emotional valence of metaphors despite literal understanding.[113] These findings, however, may not indicate specific language deficits. Alternatively, they may be explained by the better-established findings of impaired emotional processing in psychopathy.

Heterogeneity of neuropsychological findings may be partly attributable to the existence of subgroups of psychopathic individuals. For example, unsuccessful (convicted) psychopathic individuals show executive functioning deficits, whereas successful (nonconvicted) ones do not. The latter even outperformed control participants on executive functioning.[114] Thus, better executive functioning may protect a subgroup of psychopathic individuals from being detected and arrested.

Psychophysiological Correlates of PV

Psychopathic individuals are less responsive than nonpsychopathic offenders when anticipating or reacting to unpleasant stimuli, whether measured electrodermally[115] or by startle blink.[116] Measurements of event-related potentials (ERPs) show mixed results. Some P300 studies, involving a waveform linked to deployment of neural resources to task-relevant information, have been inconsistent.[117,118] Studies of other components of ERPs indicate reduced response inhibition,[119] reduced affective sensitivity for facial expressions of emotion,[120] and abnormal late negativity, maximal over frontocentral regions, with various stimulus-processing and decision-making tasks.[117] Reduced event-related negativity (a potential that peaks after an incorrect response in speeded reaction-time paradigms) has been observed in antisocial personality[121] and in psychopathic offenders,[122] possibly indicating error-detection deficits[121] or conflict-monitoring impairments.[122] However, these findings have not been replicated in other studies.[123]

Although overall baseline differences in heart rate or electrodermal arousal have not been found in individuals with psychopathy,[115] reduced heart rate reactivity to stress

has been found in unsuccessful psychopathic individuals and increased reactivity in successful ones.[114] These findings may indicate that autonomic impairments are specific to unsuccessful psychopathic individuals or that different features of psychopathy have distinct etiologies and that only the affective-interpersonal features are associated with abnormal autonomic reactivity.[124] If supported by future research, findings of diminished autonomic (especially electrodermal and startle reflex) reactivity to stressful/aversive stimuli in psychopathic individuals would be consistent with theories emphasizing their punishment insensitivity and reduced fear[125] in relationship to their affective-interpersonal capacities.[126]

Neurodevelopmental Origins and CU Traits

When brain damage occurs early in life, psychopathic-like effects are more pronounced, a finding that has been interpreted as supporting the view of psychopathy as a neurodevelopmental deficit.[46] Compared with damage acquired in adulthood, damage to the vmPFC before age 16 months has been linked to a significantly higher risk for the development of more severe abusive/criminal behaviors and reduced empathy/remorse,[59] because early damage to the vmPFC disrupts moral development.[85,127] Children and adolescents with CU traits persistently exhibit disregard for others, lack of empathy, and deficient affect. Such emotional and behavioral dysregulation distinguishes them from other antisocial youth and associates them with psychopathic adults.[128] Adolescents with high CU traits are more likely to engage in bullying,[129] to exhibit more severe instrumental aggression,[128] to be less sensitive to punishment,[130] and to expect more positive outcomes in aggressive situations[131] than conduct-disordered adolescents without CU traits.

Because of inherent ethical complications, studies on the heritability of CU traits are rare, and better research is needed to understand the genetic-epigenetic interplay.[132] A twin study of CU traits found a heritability rate of 42%, which is similar to that found in adults.[133] Another study with conduct-disordered children with high CU traits reported a higher rate of 81%.[134] Functional magnetic resonance imaging studies of children with CU traits show decreased amygdala activation in response to fear and stress,[135–137] decreased OFC-amygdala functional connectivity in moral judgments,[138] and decreased connectivity to the vmPFC, with symptom severity correlating negatively with connection strength.[139] Neuroanatomical findings include frontal alterations associated with poor decision making,[140,141] striatal structural alterations possibly associated with sensation-seeking and reward-driven behavior,[137,141] a thicker temporal cortex (particularly in male individuals),[142] and an increased incidence of cavum septum pellucidum (a marker of prenatal limbic and septal neural maldevelopment)[46]. These latter two features are interpreted as suggesting an early neurodevelopmental basis to psychopathy. In children and youth with CU traits, neuropsychological abnormalities (similar to those found in adults with psychopathy) have been found in selective attention, emotional processing, and inhibition, with reduced interference,[143] slower reaction times to negative emotional words (versus faster reactions in impulsive children/youth),[144] increased reward responsiveness,[145] and diminished response inhibition.[146] Diminished autonomic reactivity has been found in children and youth with CU traits.[147] Abnormal electrodermal response to aversive stimuli at age 3 years was found to be associated with psychopathy in adulthood,[148] and impaired electrodermal fear conditioning at age 8 years was associated with aggressive and criminal behavior 20 years later.[46] Whereas nonaggressive children show significant increases in fear conditioning from ages 3 to 8 years, aggressive children show a weaker developmental profile, implying diminished maturation of the amygdala. These findings suggest a possible early psychophysiological predisposition to the development of aggressive and antisocial behavior, providing support for a neurodevelopmental contribution to psychopathy.[46] Increased testosterone levels have been found in conduct-disordered girls[149] and adolescent boys[150] without CU traits but not in boys with CU traits.[149,151] The relationship between psychopathy and testosterone is further complicated by the fact that testosterone levels change dramatically in puberty and the effects of these changes are largely unknown. Low cortisol levels, and thus lower HPA-axis activity, have been observed in adolescents with CU traits,[151] regardless of the presence[152] or absence[153] of environmental stressors, which may significantly impair social development by reducing responsivity to stressors and decreasing the fear of negative consequences.[153]

TREATMENT OF PSYCHOPATHY/PV

Successful treatment of PV could yield enormous benefits. Psychopathic individuals are estimated to comprise 1% of the population but constitute roughly 15%−25% of the offenders in prison and are responsible for a disproportionate number of brutal crimes. Recent estimates place the national cost of psychopathy at $460 billion a year, roughly 10 times the cost of depression.[154] In the United States, the demographics are shifting toward more child and adolescent perpetrators, with increased arrest rates for youths despite decreased rates for adults.[45] The younger the perpetrators, the longer their potential active engagement in psychopathic behaviors.[45] As the following review of historical and current approaches to treating psychopathy/PV highlights, successful treatment remains an elusive goal. Potentially promising is the possibility that interventions to increase empathy could shift psychopathic individuals and youth with CU traits away from their relational characteristics of mistrust, deception, and manipulation.

Historical and Current Treatment Approaches

Can psychopathy be cured? Historically, treatment efforts have involved significant difficulties, including extremely

limited therapeutic rapport owing to a lack of bonding and high deceptiveness in this population[56]; radically limited motivation for treatment due to a lack of guilt and remorse[155]; negative treatment outcomes, with worsening of psychopathy because training of socioemotional skills may improve a psychopathic individual's criminal strategy and capacity to avoid legal detention[155]; and unreliable and simplistic measurements of treatment outcomes. The limited body of controlled outcome studies is suboptimal. Reasons include the clustering of all patients/inmates considered personality disordered, failure to control for comorbid disorders, lack of control groups, sample sizes too small for statistical significance, and generic treatment modalities.

Early treatment attempts included now-obsolete lobotomies[156] and ECT,[157] as well as punitive strategies, used in earlier community treatments, which were found to have negative effects, with youth and adults becoming more violent, more manipulative, and more likely to reoffend.[158] Pharmacotherapy is found to be efficacious in some individuals with comorbid psychiatric disorders, albeit as a result of improved mood and diminished impulsivity rather than psychopathic traits.[159] For example, lithium has been found to reduce irritability in chronically aggressive prisoners, in turn reducing their impulsive aggression, but not their predatory behaviors or overall recidivism.[160] Treatment with antidepressants (sertraline) also reduced impulsivity but not fearlessness and dominance of others.[161] Treatment with benzodiazepines had negative results,[159] presumably because of increased disinhibition and aggression. Although long-term outcomes are mostly unknown, current nonpharmacological treatments include various forms of positive reinforcement, social-skills training, anger management, and cognitive-behavioral and dialectical-behavioral therapy, implemented in prison settings or treatment communities.[162,163] Supportive and nurturing approaches are most effective in youth, thus supporting early interventions.[164,165] Outcome studies for insight-oriented psychotherapy indicate self-reported improvements that did not correlate with reduced recidivism or changes in psychological traits.[166] Although group therapy is commonly used, it lacks reliable outcome studies[167] and can even have deleterious effects.[168] More recent approaches advocate multimodal interventions, with combined individual, group, and family treatments.[164] Notably, typically little information is available about whether any reported improvements transfer to real-life situations. Overall, treatment programs specifically tailored to psychopathy and its affective and interpersonal deficits are scarce.[169,170] Efficacy of treatment is typically evaluated based on treatment compliance and recidivism,[155] rather than on any positive effects on the affective and interpersonal facets of psychopathy.[164,171]

Potential Treatments to Increase Empathy

Recent studies have begun to compare treatment of predatory versus impulsive offenders, with group classification based on volumetric measures of gray matter.[172,173] Although patients with impulsive personality traits appear to be responsive to existing therapies, traditional treatments for predatory offenders do not appear to be helpful.[173] Using volumetric measures, one study found increased empathic responding in psychopathic individuals on a task of intentional effort to empathize.[174] Other authors have advocated an overt cognitive process of attention reallocation in an effort to activate top-down triggering of empathic responsiveness. It remains unclear, however, what cognitive, psychological, and emotional processes are involved in intentional effortful empathizing and also whether direct interventions to increase empathy actually stimulate empathy or merely the mimicking of empathic responding. A potentially better approach is to activate empathic processes less directly and explicitly, thereby possibly bypassing the mistrust and deceptiveness typical of psychopathic individuals. Can the brain be trained or induced to become more empathic? In the general population, this question has been addressed from a number of perspectives.

Cognitive reframing/reappraisal therapy, requiring the imagination of positive outcomes to suffering, can increase empathic responsiveness through activation of higher cortical functions, which downregulate amygdala activation, reducing cortisol secretion and autonomic fear activation.[175] Stable and empathic attachment in anxious children can develop by priming with words, memories, or stories of secure attachment.[176] Deliberate affective regulation, with increased PFC and decreased amygdala activation,[177] suggests inhibitory top-down influences of cortical prefrontal projections to the amygdala.[178] Eight weeks of mindfulness meditation can induce neuroplastic changes in the anterior cingulate cortex, insula, temporoparietal junction, and frontolimbic network, with associated increases in attention regulation, body awareness, emotional regulation, and self-other perspective.[179,180] Although it requires years of sustained practice (but irrespective of meditator's age), long-term mindfulness training induces volumetric changes in the insula, amygdala, and right temporoparietal junction, with resulting increased empathy.[175] The significance of these findings depends on whether they can be meaningfully applied to the population of psychopathic offenders.

Any promising intervention with youth with CU traits or adults who exhibit PV would need to address both possible hypoarousal in the limbic region (associated with reduced fear and stress sensitivity, reduced responsiveness to punishment, and reduced empathic resonance) and possible neurocognitive rigidity, impaired attentional mechanisms, and impaired attachment subserved by the OFC and vmPFC. Possible hormonal and neurotransmitter imbalances further reinforcing such mechanisms must also be considered. To our knowledge, no such comprehensive treatment program has been tested or implemented to date.

DISCUSSION

Review of the neurobiology of empathy has revealed that significant aspects of empathic responsiveness are present at

birth and continue to mature throughout childhood and adolescence, in the context of interpersonal relationships. Maturation involves a progressive shift along the dorsolateral PFC-limbic pathway, from more activation of limbic structures early in development to more activation of frontal regions later in development. The extent of this shift is affected by individual predisposition toward autonomic arousal, emotional reactivity, and strength of executive functions.

Although the affective and cognitive components of empathy are dissociable, their interplay allows for emotional regulation. Mature empathic sensitivity depends on the functional integration of these components in the service of relationships and goal-directed social behavior. Social bonding, attachment, and empathy are interconnected at the neurobiological level by the modulatory effects of hormones, with increased oxytocin levels and increased HPA activity correlating positively with more secure attachment and an increased capacity for empathy. Secure attachment and empathic responsiveness alike stimulate the brain reward pathways, which become self-reinforcing.

Whereas IV has been more clearly linked to increased limbic activation with resulting heightened emotional arousal and diminished frontal activation with resulting disinhibition, PV presents a more complex profile. No single region, whether structurally impaired or functionally diminished, will result in psychopathy or in specific cognitive or affective aspects of psychopathy. A recent theoretical paradigm points to limbic hypoarousal, leading to shallow affect and diminished fear, paired with intact or even overactive frontal circuitry, resulting in increased cognitive rigidity, increased hyperattention to selective targets, and difficulties with attention shifting and flexible behavior, possibly leading to obsessive fixations and calculated actions. Further findings, although limited, suggest that psychopathic individuals' reduced fear, reduced sensitivity to punishment, enhanced sensitivity to reward, and hyporesponsivity to stressors—all of which affect their decision-making behavior—may be linked to the combined effect of reduced cortisol, increased testosterone levels, and reduced HPA activity.

The frontotemporal/limbic/hormonal interplay is likely the main factor in the emergence of PV, but this explanation may still be too simplistic. Whereas impulsive perpetrators typically feel remorse or guilt, predatory perpetrators typically do not. Instead, they tend to feel most engaged and perhaps most "alive" while executing their plans or reliving their experiences through crime-scene revisitations, photos, or other types of "souvenirs" from their crimes and in ways that suggest a radical distortion of the experience of bonding. Such distortions—which, to the best of our knowledge, are poorly understood and scarcely acknowledged—may be what ultimately lead to those behavioral expressions of PV that are described as "evil."

Such radical deficits of bonding point to a very early etiology of psychopathy and support proposed neurodevelopmental hypotheses.[46] Such hypotheses take into account the fact that psychopathic behaviors manifest early in life; continue relatively consistently during childhood, adolescence, and, overall, across time[181]; and are mostly resistant to conventional treatments.[163] Significantly, people who suffer neurological damage at a very early age exhibit characteristics that most closely resemble psychopathy, suggesting that psychopathy is associated with impairments in brain functioning before moral socialization and social bonding.[127] In addition, psychosocial, demographic, and head-injury measures alone have not accounted for the structural and functional brain impairments observed in psychopathy.[46] A neurodevelopmental hypothesis must also consider the fact that male individuals are much more likely than female individuals to commit certain types of violent crimes.[182] Female individuals tend to be more empathic as a result of their evolutionary biological role in the reproduction and care of infants.[183] This is true for female children as well, who score higher than male children in empathic concern.[184] Although they are still speculative, recent observations suggest neurodevelopmental abnormalities in both juvenile and adult psychopathic offenders.[46]

Only very recent studies have compared predatory versus impulsive offenders, basing group classification on volumetric measures of gray matter.[172,173] These studies show that whereas impulsive offenders can be treated with existing therapies, traditional treatments for predatory offenders may be useless. The interpersonal and affective aspects of psychopathy have only very recently come to the attention of treatment theories and remain to be addressed in actual interventions.

Given that mindfulness training induces neuroplastic changes in the frontolimbic network and increases emotional regulation, attentional skills, and empathic responsiveness, it potentially represents, at least in theory, a more comprehensive and targeted approach to treating the interpersonal/affective empathic deficits in psychopathy. However, because neuroplastic and behavioral changes are a slow process, requiring years of sustained mindfulness practice, this approach is likely suitable only as a very early intervention.

Within this context, the use of prospective longitudinal studies to identify and assess children and adolescents with CU traits has important implications for the prevention and management of adult psychopathy. Increasing the specificity of target theoretical constructs may increase the replicability of findings and produce more converging results. PV and IV distinction, cognitive and affective empathy dissociation, antisocial and psychopathic personality differences should all be taken into consideration in designing future research. Studies are needed that investigate the role of hormones and neurotransmitters and their interplay with neural mechanisms, as well as the precursors, risk factors, and correlates of CU traits in early infancy and in longitudinal designs.

In terms of treatment, we recommend careful assessment of participants in order to better tailor interventions. Best results may be expected when assessments and treatments take place before the second critical period of neuronal

plasticity of early adolescence[185,186] and differentially target the cognitive and affective aspects of empathic deficits in psychopathy.

Studies are needed that assess the behavioral, psychological, and neurological outcomes of mindfulness training and related types of cognitive-behavioral therapies among incarcerated youth who do or do not exhibit CU traits and/or PV. Such studies should aim to evaluate changes in neural connectivity, cognitive function, cortical thickness, affective reactivity, self-regulation, and social relationships as a result of treatment. This has the potential to uncover an important behavioral intervention, with implications for neural plasticity.

More broadly, we hope that the growing understanding of the neurobiological basis of PV and associated criminal behavior encourages a dialogue on the role of neuroscience in criminal justice, on the implications for punishment versus potential prevention and treatments, and on prediction of violence and risk assessment[187] and leads to educational outreach efforts to targeted audiences spanning legal, scientific, and policy fields.

CONCLUSIONS

The behavioral expressions of empathy in bonding, attachment, and prosocial behaviors and of deficits in empathy in PV and psychopathic behaviors share significant neural substrates. This, in turn, points to a new way of thinking about their genesis.

Empathic processing is primarily related to the homeostatic functioning of the OFC/vmPFC-limbic pathways and to the reciprocal influence of the HPA axis, oxytocin, and brain reward mechanisms. CU traits, PV, and psychopathic behaviors are tightly linked to these same structures. The functional imbalance of the OFC/vmPFC-limbic pathways leads to the cognitive and interpersonal/affective aspects of psychopathy. Diminished HPA activation and reduced cortisol levels result in increased stress tolerance and diminished fear. This may also potentially affect the ongoing capacity to form attachments and activate the brain reward system during interpersonal interactions. Thus, the inverse relationship between empathy and PV shares similar neuroanatomical substrates. A corollary of this is that strengthening empathy, which enhances bonding, might result in diminished PV.

Individuals with psychopathy are typically viewed as resistant to treatment. Significant conceptual advances have occurred in recent years, particularly regarding the relationship between PV and empathy. Our review suggests that more targeted interventions aimed at specific features of psychopathy might lead to better outcomes, with maximal effectiveness in the context of very early interventions. Continued efforts to identify, assess, and treat children and adolescents with CU traits have important implications for preventing and managing adult psychopathy. Although the specific aspects of deficiencies in empathic processing in psychopathy remain poorly understood, it is clear that an important relationship exists between empathy and PV, which may be essential in the development of treatments for this disorder.

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