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Using Neuroscience to Make Sense of Psychopathy

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In 1989, 42-year-old Ted Bundy was executed by electric chair following his conviction for multiple counts of first-degree murder. Prior to his death, Bundy confessed to killing 30 individuals, many of whom were young women. The true number may have been much higher. The heinous details of his crimes—including assault, kidnapping, rape, and necrophilia— shocked the public, as did the cold-hearted way he carried them out, seemingly devoid of any empathy or remorse. Bundy admitted to meticulously plotting the gruesome crimes with little to no consideration for the suffering of his victims (1). He is often held up as the archetypal psychopath.

In recent years, there has been increased discussion of psychopathy in the media, fueled by ongoing stories relating to high-profile individuals in the finance sector, in entertainment, and in politics. Their stories are endlessly explored in books, films, and public conversation as society struggles to make sense of the seemingly inexplicable. Ultimately, discussion circles back to the same two questions: what was going on in their heads, and why did they do it?

Long before modern psychiatry, neuroscience, or even the concept of psychopathy existed, scientists were interested in what makes people behave aggressively. A seminal early finding emerged from an unfortunate accident. In 1848, a tamping iron slammed through Phineas Gage's left cheek, destroying large parts of his medial prefrontal cortex (PFC). Suddenly, his personality transformed from one of agreeableness and civility to one of argumentativeness, unpredictability, lying and impulsivity, and easily provoked aggression. Gage's accident provided some of the first clues of the crucial role of the frontal lobes in regulating aggression and other social behaviors.

In the century after Gage's accident, neuroscientists turned to animal models to further explore the underpinnings of aggression (2). In the 1890s, German physiologist Friedrich

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Leopold Goltz ablated the cerebral cortex (as well as parts of the neostriatum and dorsal diencephalon) of dogs; when lifted from their cages, the previously passive pups were transformed into savage beasts, growling, barking, and biting. Later experiments looked at a similar phenomenon in cats (coined “sham rage”) and found that an intact hypothalamus was essential to produce the physiological correlates of aggressive behavior (3). Similar localization work continued through the subsequent decades, with various studies implicating the hypothalamus, the midbrain periaqueductal gray, and limbic structures (including the amygdala).

Perhaps most interestingly, the experiments started to reveal that it might not be a single region per se that influenced aggressive behavior, but rather the communication between regions. For instance, in an elegant series of experiments, German neuroscientist Robert Hunsperger demonstrated that the rage response normally elicited by stimulating the medial hypothalamus in cats could be blocked by ablating part of the periaqueductal gray (2). Evidence was converging on a unifying hypothesis: aggression is not localized to a specific region, but instead arises from a complex interaction among structures.

Contemporaneous with these animal experiments, a young psychiatrist named Hervey M. Cleckley began studying a clinical phenomenon with a hallmark of violent behavior. Through his work in a large neuropsychiatric hospital, he was fascinated by patients who superficially appeared “normal” but who covertly engaged in criminal and destructive acts. He revived the term “psychopath,” originally used in the late 19th century to describe individuals with mental illness and dangerous behaviors, to describe these patients. Based on indepth interviews, Cleckley devised a psychopathy classification scheme that included not only aggression but also traits like superficial charm, above-average intelligence, the absence of delusions or generalized anxiety, insincerity, lack of shame or remorse, poor judgment and an inability to learn from experience, and a lack of insight into their behavior. These symptoms ultimately gave rise to the current DSM criteria for antisocial personality disorder. In his groundbreaking work *The Mask of Sanity* (4), Cleckley concluded that psychopaths posed a significant threat to society because they hid well but comprised the majority of serial killers and conmen.

Limited by the rudimentary tools at his disposal, Cleckley could only guess at the underlying etiology of psychopathic behavior. He speculated that like patients with semantic aphasia, who lose the connection between words and their meaning, psychopaths may analogously suffer a “semantic dementia”—a disconnect between behavior and its social and affective meaning.

This core idea—that individuals with psychopathy may differ in their ability to integrate affective and other information into behavior—has continued to animate research to this day. Because one of the most salient aspects of psychopathy is blunted affect, much of the recent research has focused on this domain. Over the past decade, imaging studies have consistently demonstrated anatomic and functional differences both within and between the ventromedial PFC (vmPFC) and the amygdala in individuals diagnosed with psychopathy (5). Broadly speaking, these findings have been interpreted as underlying some of the

interpersonal and affective aspects of the disorder (e.g., callous-unemotional personality and lack of remorse). Of note, this work has largely focused on the negative valence system.

Following this work, a group led by Harvard researcher Joshua Buckholtz set out to explore a related but distinct question: Could dysregulation between the PFC and the limbic system also involve the dopaminergic structures subserving impulse control and reward? To answer this question, they devised a series of behavioral experiments to explore how individuals with psychopathy process regret. The experiments used a counterfactual decision-making paradigm in which participants had to select between two "wheels," each with a different probability of gaining or losing points. The researchers looked at both how subjects responded to feedback about prior decisions and how this feedback shaped prospective decision making. They found that individuals who scored higher on a psychopathy scale reported greater retrospective regret when informed that they had selected incorrectly but were less likely to change their behavior prospectively based on the feedback (6). These results supported the idea that, behaviorally, psychopathy is associated with a disconnect between emotion and logical decision making. To better understand the neurobiological correlates, they then went to where psychopathy may be most prevalent: prisons.

In collaboration with researchers in Wisconsin and New Mexico, the team brought a mobile magnetic resonance imaging scanner to two medium-security prisons and scanned 49 inmates while they completed a reward delay discounting exercise—accept a smaller amount of money now or wait to receive a larger sum. Behaviorally, consistent with previous findings, they found that individuals with higher psychopathic traits overvalued immediate rewards. Correspondingly, they found heightened activation of the nucleus accumbens in this group (7). But perhaps the most intriguing aspect of the study was why; when they looked at associated brain regions, they found that the connection between the vmPFC and the nucleus accumbens was noticeably weak. Thus, as with previous findings relating to the amygdala, the increased activation of the nucleus accumbens appeared to reflect inadequate inhibition from the vmPFC.

Nearly 80 years after *The Mask of Sanity*, these recent data seem to support Cleckley's prescient hypothesis. The semantic dementia he described—a disconnect between behavior and emotion—may reflect failure of the vmPFC to regulate multiple limbic structures, including the amygdala, causing dysregulation of negative affect, and the striatum, leading to impulsivity and aberrant reward processing. Together, these findings offer a circuit-level model of psychopathy.

What are the practical applications of these findings? One obvious question is whether this model could be used to predict criminal behavior. A group from the University of New Mexico recently found that among inmates who underwent functional magnetic resonance imaging shortly before their release, those below the 50th percentile of activation of the anterior cingulate cortex (like the vmPFC, involved in behavioral planning) had a 2.6-fold higher rate of being rearrested (8). Though we are (thankfully) still far from the dystopia depicted in the film *Minority Report*, neuroscientific advances may improve our ability to identify those at highest risk for criminal offense. The ethical implications of such testing would be profound, including balancing public safety with the need to avoid discrimination

based on biological attributes (especially when risk would be intrinsically probabilistic). More significantly, if conducted with caution, these research findings might point the way toward effective treatment [as in a recent pilot study by Baskin-Sommers *et al.* (9)].

While these data may shed light on the question of what was going on in the heads of these individuals with psychopathy, they do little to answer why or address the existential terror these stories induce. Ongoing research is building on these circuit-level findings and exploring other domains (e.g., genetics, gene–environment interactions, and endocrine and autonomic systems) (10). Developing treatments for individuals with psychopathy may mitigate the long-term costs to society. A more effective strategy may be to implement policies with the potential to address risk factors that may lead to the development of psychopathy, like early adverse experiences. In the meantime, to ensure public safety and simultaneously respect the rights of those who are at high risk for violence, policymakers should continue to advance a just and effective system of checks and balances so that we can effectively respond to and contain dangerous behavior.

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