The neurobiology of psychopathy

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Psychopathy is a serious personality disorder characterized by emotional and behavioral abnormalities. The disorder is present in approximately 15-20% of criminal offenders [3] and is one of the strongest predictors of violent recidivism in prisoners [4]. Psychopaths tend to lack of feelings of empathy, guilt, and remorse; they often lack fear of punishment, are impulsive, have difficulty regulating their emotions, and display antisocial and violent behavior. Psychopaths may use superficial charm, conning, and manipulation to take advantage of others. A unique feature of psychopathy is that, in addition to increased reactive aggression, they also display instrumental aggression [5]. Psychopathy encompasses a variety of personality and behavioral features, as demonstrated by the 20-item rating scale, the Psychopathy Checklist—Revised (PCL-R) [5] that has emerged as the gold standard for assessing psychopathy. The scale has traditionally been divided into two factors, with Factor 1 describing the interpersonal and affective features and Factor 2 describing socially deviant behaviors, though three- and four-factor models have also been proposed [6] [5]; thus it becomes clear that many of the features of psychopathy are relatively distinct and from different domains.

It is perhaps this “constellation” of features [7], which contribute to the seemingly widespread neurobiological deficits observed in psychopathy. Several brain imaging studies have explored structural and functional differences in the brains of psychopaths, but very few have begun to look at the role of genetic factors or neurotransmitter or neuroendocrine functioning; thus, the field is still far from a molecular neuroscience account of psychopathy [8]. While psychopathy has thus far been found to be intransigent to treatment attempts [9], an understanding of the neural substrates of psychopathy will likely be a major contributor to future treatment and prevention.

NEUROTRANSMITTERS

In highly studied areas of psychopathology such as depression and schizophrenia, neurobiological research has advanced to the level of examining pathology at the level of neurotransmitter systems. To the author’s knowledge, only a few studies have examined the role of neurotransmitters in the development and maintenance of psychopathy. In two independent samples, Soderstrom et al. [10,11] found that psychopathy was associated with an increased ratio between the dopamine metabolite HVA and the serotonin metabolite 5-HIAA. This increased ratio is thought to be an indicator of impaired serotonergic regulation of dopamine activity, which results in the disinhibition of aggressive impulses. It is suggested that dopamine modulating drugs, possibly in combination with serotonin reuptake inhibitors might be potential pharmacologic treatments for psychopathy.

Reciprocal relationships have been shown to exist between neurotransmitter and endocrine systems. For example, serotonin neurotransmission has an effect on the hypothalamic-pituitary-adrenal (HPA) axis so that increased activity at serotonin receptor sites in the hypothalamus increase the production of cortisol. Sobczak et al [12] found that disruption of serotonin neurotransmission disrupts cortisol reactivity to a stress-inducing speech task. Thus, dysregulation of serotonin in the brain may contribute to the low cortisol levels observed in psychopathy. However, evidence also suggests that cortisol can have an effect on serotonin transmission in the brain [13]. Given the interdependence of these systems, it becomes highly difficult to localize a specific system that contributes to psychopathic characteristics; it is likely that a complex pattern of brain activity is involved.

Serotonin may also interact with testosterone levels to increase the probability of violent aggression. Evidence suggests that low serotonin levels combined with high testosterone levels augment the rates and intensity of aggression [14]. A recent review of the literature suggests that elevated testosterone alone does not account for aggressive behavior, as it is often observed in successful athletes and businessmen who are not necessarily more violence-prone; testosterone is more strongly associated with dominance than aggression [15]. It is hypothesized that elevated testosterone levels
encourage dominance-seeking behaviors, yet when an individual becomes frustrated in an attempt to achieve dominance, low serotonin levels may increase the likelihood of an aggressive response. Low serotonin levels have been associated with impulsive and highly-negative reactions, and thus may increase the tendency for violent aggression [15].

While early evidence suggests that dysregulation of neurotransmitter systems may be involved in psychopathy, additional studies are needed to explore this relationship and its implications further. Because neurotransmitters can interact with neuroendocrine systems, as well as affect the functioning of certain brain regions, it is important to gain an understanding of the role they may play in the development and maintenance of psychopathy.

**NEUROENDOCRINOLOGY**

In an analysis of recent research, Van Honk et al. [2] propose that the underlying source of emotional deficits observed in psychopathy are a result of an imbalance of the hormones cortisol and testosterone. Cortisol is a glucocorticoid hormone that is released upon activation of the hypothalamic-pituitary-adrenal (HPA) axis. The role of cortisol is to mobilize the body's resources and to provide energy in times of stress [16]; it is also involved in potentiating the state of fear [17], sensitivity to punishment, and withdrawal behavior [18]. Testosterone is a product of the hypothalamic-pituitary-gonadal (HPG) axis and is associated with approach-related behavior, reward sensitivity, and fear reduction [19]. Testosterone and cortisol have been shown to have mutually antagonistic properties. Cortisol suppresses the activity of the hypothalamic-pituitary-gonadal (HPG) axis on all levels, diminishing testosterone production and inhibiting its effects [20]. In turn, testosterone inhibits activity of the HPA axis [21]. Van Honk and colleagues have found that injections of testosterone reduce fearfulness [22], promote responding to angry faces [23], and shift the balance from punishment to reward sensitivity [24]. In the latter study, Van Honk et al. found that a single administration of testosterone led to disadvantageous decision making in the Iowa gambling task, with participants showing decreased sensitivity to punishment and increased sensitivity to reward; thus, by manipulating the balance between cortisol and testosterone, critical changes can be observed in an individual’s decision making behavior. Van Honk [2] proposes that low levels of cortisol, accompanied by high levels of testosterone, might contribute to primary psychopathy.

A few studies have found relationships between cortisol and psychopathy. Holi et al. [25] measured serum cortisol levels in young adult male psychopathic offenders with a history of violence and found a negative correlation with psychopathy, although the sample size was small. Low salivary cortisol levels were also observed in adolescents with callous-unemotional traits, which are thought to be similar to psychopathic traits in adults [26]. In a study of undergraduates, O’Leary et al. [27] found that males scoring higher in psychopathy showed less cortisol reactivity to a social stress test than lower scoring males.

While several studies have explored the link between testosterone and aggression, very few studies have examined the relation between testosterone levels and psychopathy specifically. Stalenheim et al. [28] found that testosterone levels were positively related to scores on Factor 2 of the PCL-R, although it is possible the results may be confounded by comorbid substance abuse and other psychiatric disorders. Loney et al. [26] examined testosterone levels in boys with callous-unemotional traits, which are thought to be analogous to psychopathic traits in adulthood, but found no effects. In other antisocial and aggressive groups, higher testosterone levels have been found in girls with conduct disorder [29], adolescent boys with externalizing behaviors [30], young criminals [31-33], criminal women [34], and have been associated with a variety of antisocial behaviors including difficulties on the job, nonobservance of the law, marriage failures, drug use, alcohol abuse, and violent behaviors [35]. It remains unclear, however, whether high testosterone levels are present in psychopaths.

In addition to exploring cortisol and testosterone levels in psychopathy, future studies may also want to examine the distributions and sensitivity of different receptors. For example, depression has been associated with an increased ratio between two different types of cortisol receptors, and also with decreased sensitivity in one type of receptor. Thus, it may be important to explore different aspects of neuroendocrine functioning in psychopathy.

Hormones have an effect on behavior by inducing chemical changes in specific brain regions, thus affecting the likelihood of certain behavioral outcomes by modulating neural pathways. In addition, both neurotransmitters and hormones are expressed at early periods of neural development, so it is likely that they participate in the structural organization of the nervous system [15]. Several studies have found differences in the structure in specific brain regions and networks, yet the underlying factors that may cause or maintain these abnormalities remains unknown.
SUBCORTICAL BRAIN STRUCTURES

It has been argued that dysfunction in the amygdala is central to the pathology associated with psychopathy [36]. Specifically, impaired amygdala functioning disrupts the ability to form stimulus-reinforcement associations, hindering the individual from learning to associate their harmful actions with the pain and distress of others. The amygdala is also necessary for aversive conditioning and for enhancing attention to emotional stimuli, which facilitates empathy for victims [1]. Psychopathy is associated with deficits in aversive conditioning [37], fearful facial expression recognition [38], passive avoidance learning [39], and augmentation of the startle reflex by visual threat primes [40]. Each of these deficits has also been associated with lesions to the amygdala [41].

Brain imaging studies of psychopathy have revealed structural and functional abnormalities in the amygdala. Reduced volume of the amygdala has been reported in a study of psychopathic individuals [42]. In several fMRI studies, reduced activity in the amygdala has been associated with psychopathy during the processing of emotional stimuli [43], during fear conditioning [44,45], during a socially interactive game [46], and during an affect recognition task [47]. However, two studies have reported increased amygdala activation in antisocial individuals while viewing negative visual content [48] and during aversive conditioning [49].

The source of impaired functioning in subcortical structures such as the amygdala remains to be elucidated, but impairments likely occur early in life [8]. One possibility is that hormone imbalances prenatally or in early childhood affect the development of subcortical structures, and may continue to influence functioning into adulthood [2]. A major binding site for steroid hormones is in the amygdala. Here, hormones have been shown to affect gene transcription, and therefore have the ability to affect functioning by increasing or decreasing the probability of certain responses such as approach or withdrawal behavior in response to threat [18].

Genetic and neurotransmitter factors may also affect amygdala functioning. Blair [50] highlights a study showing that individuals who are homozygous for the long version of the serotonin transporter gene (5-HTTLPR) show significantly reduced amygdala responses to emotional responses to emotional expressions relative to those with the short-form polymorphism [51] and behavioral impairment on emotional learning tasks that depend on the amygdala [52]. The amygdala has many serotonergic inputs and thus may be sensitive to changes in serotonin transmission.

In addition to the amygdala, abnormalities have also been observed in other subcortical regions such as the hippocampus. Raine et al [53] found asymmetries within the hippocampus in unsuccessful (convicted) psychopaths. Hippocampal dysfunction may result in affect dysregulation, poor contextual fear conditioning, and insensitivity to cues predicting capture. Atypical brain asymmetries are thought in part to reflect disrupted neurodevelopmental processes [54]. Brain asymmetries first appear during fetal development, but tend to decrease somewhat with age in normal children [55]. Structural asymmetries in psychopaths may reflect an interruption to the normal developmental process. Lakko et al. [56] found psychopathy to be negatively correlated with the volume of the posterior hippocampus. The hippocampus has dense interconnections to both the amygdala and prefrontal cortex, which have also been implicated in psychopathy, so it may have an effect on and be affected by the functioning in these structures.

CORTICAL BRAIN STRUCTURES

Raine et al [57] observed an 11% reduction in prefrontal gray matter volume in a group of individuals with antisocial personality disorder compared to both normal and psychiatric control groups. Furthermore, the individuals with antisocial personality disorder showed reduced skin conductance activity during a social stress test, and those with particularly low prefrontal gray showed particularly reduced stress reactivity. This study supports evidence that prefrontal regions, in particular the orbitofrontal cortex, are involved in generating somatic states. Indeed, Van Honk et al [58] provided further evidence for this by using repeated transcranial magnetic stimulation (rTMS) to inhibit the activity of the orbitofrontal cortex and found that it resulted in significant reductions in skin conductance responding.

An additional finding of reduced prefrontal gray matter in psychopathy was later observed in a group of unsuccessful psychopaths, demonstrating a 22.3% reduction in gray matter [59]. Two studies have shown reduced gray matter volumes specifically in the orbitofrontal cortex in antisocial individuals [60,61]. Functional imaging studies have observed reduced activity associated with psychopathy in the orbitofrontal cortex during fear conditioning [44,45], and during a socially interactive game [46]. The orbitofrontal cortex is associated with the anticipation of punishment and reward, response reversal during changing reinforcement contingencies, as well as social cognition in general [62,63]. Lesion studies have demonstrated that damage to the orbitofrontal cortex often results in pathologic lying, irresponsibility, promiscuous sexual behavior, shallow affect, and a lack of guilt or remorse [64], all of which are characteristics of psychopathy.
Several studies have observed increased activation in higher cognitive areas such as the dorsolateral prefrontal cortex during emotional tasks in psychopaths compared to controls [43,46,47,65]. It has been suggested that psychopaths may use more cognitive resources to process affective information than nonpsychopaths [43].

OTHER STRUCTURES

While abnormalities in the amygdala and orbitofrontal regions are the best replicated, psychopathy has also been associated with abnormalities in other regions. Reduced functioning in the anterior cingulate has been observed during fear conditioning [44,45], in criminal psychopaths during an affective memory task [43], and in processing of emotional information [48]. The anterior cingulate is closely connected with the amygdala and is involved in emotional processing. Deficits in the angular gyrus (posterior superior temporal gyrus) have been found in psychopathic and antisocial individuals during a semantic processing task [66] and functioning of the posterior cingulate, which may be involved in self-referencing and experiencing emotion, has been observed in an fMRI study of psychopaths [43]. Reduced functioning of the insula has been observed during fear conditioning [44,45]; the insula is thought to be involved in the emotional processing of anticipatory anxiety and awareness of threat stimuli and associated body states [67]. Kiehl [68] argues for a paralimbic system dysfunction of psychopathy. In a thorough review of the literature, Kiehl points out that the seemingly distinct regions implicated in psychopathy, including the amygdala, parahippocampal region, anterior superior temporal gyrus, insula, anterior and posterior cingulate, and the orbitofrontal cortex share similar cytoarchitecture and have been grouped together to form the “paralimbic system.” It is acknowledged that it remains unknown how or when the abnormalities in these brain regions arise. Indeed, it is difficult to determine whether each region that has been found to be associated with psychopathy makes a unique contribution to the disorder, or whether reduced input from key regions such as the amygdala or orbitofrontal cortex results in reduced functioning in other areas that are highly connected to these regions.

CONNECTIVITY

In addition to the abnormal functioning observed in certain brain regions of psychopaths, some studies have also explored the connectivity between areas. Van Honk & Schutter [2] hypothesize that disruptions in the connectivity between subcortical and cortical regions may contribute to psychopathy. Such connectivity allows emotional information from subcortical regions such as the amygdala to provide input to cortical regions, which is important in guiding decision-making and cognitive evaluation [69]. Connectivity between the amygdala and orbitofrontal cortex may be especially important in the generation of somatic markers. The orbitofrontal cortex receives emotional input from the amygdala and stores representations of certain events or stimuli so that they can be retrieved later. If an individual then recalls or anticipates these events or stimuli, the orbitofrontal cortex triggers the somatic state. If connectivity between the amygdala and orbitofrontal cortex and amygdala is disrupted, the orbitofrontal cortex will be unable to form representations and feelings such as anticipatory fear of aversive events will not be generated [70]. Indeed, reduced connectivity between the orbitofrontal cortex and the amygdala has been associated with lower sensitivity to threat cues (Harm Avoidance) [71]. The orbitofrontal cortex is also involved in dictating emotion regulation through inhibitory connections to the amygdala and anterior cingulate [72]; therefore, poor connectivity between these regions would also result in reduced regulation of subcortical structures by prefrontal areas. This may contribute to the disinhibition and reactive aggression observed in psychopathy.

Van Honk & Schutter [2] argue that an imbalance between cortisol and testosterone reduces subcortico-cortical communication. Cortisol has been shown to increase the exchange of information between subcortical and cortical brain regions and strengthen cortical control over subcortical drives [73]. In contrast, testosterone administrations have been shown to reduce subcortical-cortical cross-talk [74]. Since the frontal cortical areas rely on subcortical areas for emotion-related information, it is argued that the decoupling results in cortical processing that is purely cognitive, and thus cold and instrumental [2]. However, it remains to be seen whether connectivity between subcortical and cortical regions is disrupted in psychopathy.

In addition to subcortico-cortical connectivity, psychopaths may also exhibit impaired connectivity between the two hemispheres of the brain. Recently, Hiatt & Newman [75] found that the time required to transfer information from one hemisphere to the other is significantly prolonged in criminal psychopaths compared to criminal non-psychopaths. This effect was more pronounced in right-handed response conditions, which are controlled by the left hemisphere. They suggest that impaired connectivity between hemispheres may cause functions primarily mediated by the left hemisphere (e.g. approach behavior and language processing) to be relatively unmodulated by functions mediated predominantly by the right hemisphere (e.g. behavioral inhibition and emotion processing) and vice versa. While this hypothesis remains to be tested, it may prove to be an important link in explaining several seemingly distinct phenomena observed in
psychopathy. Further evidence for impaired connectivity between hemispheres comes from a structural imaging study by Raine et al. [76] that found increased volume of the corpus callosum in psychopathic individuals. The corpus callosum is the major connection between the two hemispheres. Future imaging studies may help to further our understanding of the connectivity between hemispheres in psychopaths. Diffusion tensor imaging (DTI) can be used to trace fiber pathways between hemispheres, while functional imaging may help to examine the relationships between functioning of interconnected regions.

DEVELOPMENT

Neurobiological abnormalities associated with psychopathy appear to be widespread throughout the brain. Research has come a long way in examining different structures or groups of structures and how their abnormal functioning might contribute to psychopathic characteristics, yet many unanswered questions remain. It remains unclear how structural and functional brain abnormalities, as well as hormone and neurotransmitter imbalances, originate. It is also unknown how different system interact to maintain a particular pattern of brain functioning.

Research suggests that psychopathic features are present at an early age, with indicators of temperamental and psychophysiological differences being detected as early as age 3 in individuals who develop psychopathic traits in adulthood [77]. Furthermore, a growing body of evidence is suggesting that psychopathic traits are identifiable in childhood [78,79]. Such research suggests that neurobiological impairments occur very early in life.

TREATMENT

Taking into consideration the recent developments in understanding the neurobiology of psychopathy, it would be predicted that potential treatments could aim to increase the functioning of key brain regions. This might be achieved in a variety of ways, including pharmacological mechanisms that might alter neurotransmitter or endocrine balances, or techniques that might directly alter the functioning of certain brain regions. Van Honk & Schutter [2] have suggested that pharmacological therapies that would restore the homeostatic balance between cortisol and testosterone could potentially help to sensitize a psychopath’s emotional responsiveness so that behavioral therapies that previously failed may gain efficacy. A method that might directly alter the functioning of certain brain regions is repetitive transcranial magnetic stimulation (rTMS), a non-invasive technique that is used to stimulate the brain using very strong, pulsed magnetic fields; this results in changes in cortical excitability in the stimulated area. While research using the technique is still in its infancy, rTMS has been studied as a potential treatment for affective disorders, particularly depression, and in some cases has demonstrated results superior to placebo [80]. Depression has been associated with increased activity in the orbitofrontal cortex [81]. In a sample of depressed patients, Shutter and Van Honk [82] demonstrated that inhibitory rTMS over the left orbitofrontal cortex enhanced memory for happy faces in depressed patients, presumably by inhibiting activity in this area. The potential use of rTMS in the treatment of psychopathy remains to be studied. Potentially, rTMS could be used to enhance functioning of the orbitofrontal cortex and help to reduce impulsive tendencies. Knoch et al [83] has shown that fast rTMS applied to the right dorsolateral prefrontal cortex increases activity in the orbitofrontal cortex bilaterally. As the orbitofrontal region has been associated with generating somatic markers such as anticipatory skin conductance responses to aversive stimuli, perhaps enhancing functioning of the orbitofrontal cortex could help to activate the autonomic system in psychopaths.

Finally, while psychopathic individuals tend to be resistant to treatment relative to other disorders, researchers in the field may be able to gain insight from understanding the neurobiology and biological treatments of other disorders. For example, depression has been linked to most of the same structures that have been implicated in psychopathy, but in the opposite direction. Depression has been associated with hyperactivation in areas such as the amygdala, hippocampus, ventromedial prefrontal cortex, and anterior cingulate. As in psychopathy, it has been proposed that the connectivity between limbic and cortical areas may be disrupted, compromising the cross-talk between regions. Hyperactivity of the limbic system leads to stimulation of the hypothalamus, resulting in imbalances in the endocrine system, including increased cortisol levels [84]. Future research in psychopathy may benefit from paying attention to ongoing research on seemingly unrelated psychopathology. An exploration of the factors that may cause some individuals to develop hyperactivity in certain brain regions while others experience hypoactivity may provide essential clues to the development of psychopathy and other disorders. In addition, by examining the effects of various pharmacologic and behavioral treatments for disorders such as depression, we may be able to form new hypotheses about possible treatments for psychopathy.

SUMMARY
It is becoming increasingly clear that understanding the neurobiology of psychopathy goes far beyond identifying brain regions that may be involved. Genetics, neurotransmitters, and hormones all impact the functioning of brain structures and the connectivity between them. In future research it will be important to identify how these systems work together to produce the unique compilation of traits and behaviors characteristic of psychopathy. Finally, by considering the similarities and differences between psychopathy and other disorders of emotion, we may be able to gain insight into possible mechanisms that produce and maintain the disorder, as well as potential methods of treatment.

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