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## Structural Brain Abnormalities in Psychopaths—a Review

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The biological basis of psychopathy has not yet been fully elucidated. Few studies deal with structural neuroimaging in psychopaths. The aim of this article is to review these studies in order to contribute to our understanding of the biological basis of psychopathy. Data in the literature report a reduction in prefrontal gray matter volume, gray matter loss in the right superior temporal gyrus, amygdala volume loss, a decrease in posterior hippocampal volume, an exaggerated structural hippocampal asymmetry, and an increase in callosal white matter volume in psychopathic individuals. These findings suggest that psychopathy is associated with brain abnormalities in a prefrontal-temporo-limbic circuit—i.e. regions that are involved, among others, in emotional and learning processes. Additionally, data indicate that psychopathic individuals cannot be seen as a homogeneous group.

The associations between structural changes and psychopathic characteristics do not enable causal conclusions to be drawn, but point rather to the important role of biological brain abnormalities in psychopathy. To gain a comprehensive understanding of this, psychopathy must be viewed as a multifactorial process involving neurobiological, genetic, epidemiological and sociobiographical factors. Copyright © 2008 John Wiley & Sons, Ltd.

### THE CONCEPT OF PSYCHOPATHY

“Psychopathy” can be seen as a special subtype of personality disorder. The concept of psychopathy was first discussed in the scientific literature in the 19th century by the French psychiatrist Philippe Pinel, with his designation of a “*mania sans délire*” (“madness without delirium”). Pinel used this term to describe individuals who are characterized by a lack of morality and behavioral control occurring despite the

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absence of any psychotic symptoms or deficits in intellectual functions. Later in the 20th century, a highly influential contribution was made by Hervey Cleckley with his book *The Mask of Sanity* (1976), in which he described psychopathy as a constellation of specific interpersonal, affective and behavioral features. Hence, besides leading an antisocial lifestyle, psychopaths are characterized as selfish, domineering, manipulative, irresponsible, impulsive, fearless, shallow, callous as well as lacking empathy and remorse. Therefore, psychopathy is not restricted to individuals showing criminal or deviant behavior, but can also be found in socially well adjusted and successful individuals.

Hare operationalized Cleckley's criteria of psychopathy with his Psychopathy Checklist and its revised edition (Psychopathy Checklist—Revised, PCL-R; Hare, 1991), a standardized semi-structured interview. The PCL-R score is based on two factors: Factor 1, “emotional detachment”, including items that describe a cluster of affective–interpersonal traits, so-called core personality traits of psychopathy, for example callousness, manipulateness and remorselessness, while Factor 2, “antisocial behavior”, represents a history of antisocial behavior, impulsiveness, and violence. Some authors also report a three-factor structure (arrogant/deceptive, affective and impulsive/unstable; Cooke & Michie, 2001). The PCL-R currently represents the most widely accepted diagnostic instrument for psychopathy.

It is important to note that the term “psychopathy” is not synonymous with the DSM-IV concept of the “antisocial personality disorder” (APD). As shown in Figure 1, psychopaths form a special subgroup of the antisocial personality disorder.

Unlike the concept of psychopathy as operationalized by Hare's PCL-R, the DSM-IV criteria of an antisocial personality disorder are mostly restricted to the description of criminal and socially deviant behavior. Therefore, while a psychopath scores highly on both factors of the PCL-R, someone with an antisocial personality disorder will score highly on Factor 2 (antisocial behavior). The diagnosis of an antisocial personality disorder can hence be applied to the majority of prison inmates. Nearly 75% of prison inmates fit the DSM-IV criteria describing an antisocial personality disorder, while the prevalence of psychopathy is much lower, namely about one-quarter of the 75% prison inmates with APD (Hare, 1998). It is

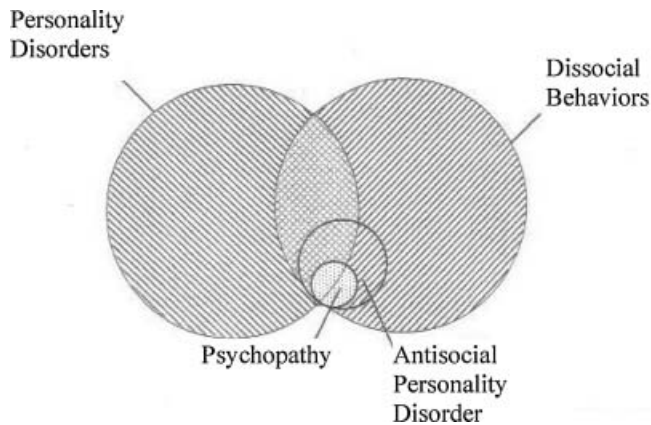


Figure 1. The classification of the concept of “psychopathy” (Herpertz & Saß, 2000, p. 571; © (2000) John Wiley & Sons Limited. Reproduced with permission).

noteworthy, however, that reported international prevalence rates of antisocial personality disorder among prison inmates differ considerably. Whereas, in a study of German prisoners, Schönfeld et al. (2006) reported prevalence rates of antisocial personality disorder of nearly one-third in both incarcerated female and male subjects, Fazel and Danesh (2002) found an average prevalence rate of 47% in incarcerated male subjects and 21% in incarcerated female subjects in western countries.

Furthermore, research shows that some individuals with psychopathy also meet the criteria for additional personality disorders, in particular for paranoid, narcissistic and borderline personality disorders (Blackburn & Coid, 1998).

## **HISTORY OF NEUROIMAGING IN PSYCHOPATHS**

The search for structural brain abnormalities in psychopaths can be traced back to the Italian psychiatrist and criminologist Cesare Lombroso (1876). Influenced by the theory of phrenology put forward by Franz Joseph Gall, who pioneered the notion that different mental functions are localized in different parts of the brain, Lombroso popularized the concept of a “born criminal”. He believed that certain individuals with a “criminal mind” can be identified by “deformations of their skulls” and also other parts of their body. Lombroso’s theory has been scientifically discredited, but he had the merit of directing scientific attention to the idea of the “criminal mind”.

Interest in this area was aroused by the case of Phineas Gage in 1848. Phineas Gage, a 25-year-old railway worker, experienced severe brain injury when an iron rod passed through his skull, damaging the prefrontal cortex, mainly the orbitofrontal cortex (Figure 2). It is reported that Gage survived this accident without any major impairment in perception, cognition, memory, intelligence, motor function or speech. However, the accident resulted in a profound change of Gage’s personality: Prior to the injury Gage was described as even-tempered, responsible and kindly, whereas afterwards he was characterized as moody, impatient and disrespectful (O’Driscoll & Leach, 1998). Furthermore, an impairment of his decision-making abilities was noticeable. Gage’s case is cited as being one of the first pieces of evidence that damage to the frontal cortex, especially the orbitofrontal cortex, could alter aspects of personality and impair socially appropriate behavior.

## **“ACQUIRED SOCIOPATHY” AND “DEVELOPMENTAL PSYCHOPATHY”**

Case studies such as Phineas Gage’s, which reported the onset of a “psychopathic-like behavior” after frontal lobe injury, led to the introduction of the concept of “acquired sociopathy” (according to Blumer and Benson (1975) also termed “pseudopsychopathy”). Patients with “acquired sociopathy” show socially inappropriate and aggressive behavior after frontal brain lesion. Blair (2003) mentioned that this aggression is almost exclusively reactive (impulsive) compared with the more instrumental, goal-directed aggression shown by individuals with “developmental” psychopathy (although the distinction made between these two

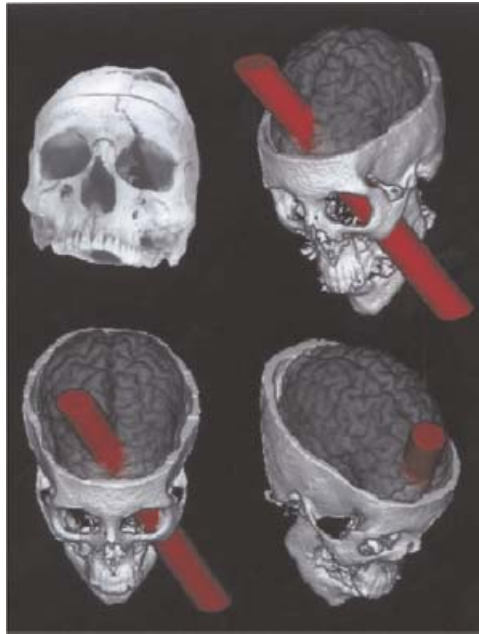


Figure 2. Reconstruction of the lesion suffered by Phineas Gage, in which an iron bar passed through his prefrontal cortex (Dolan, 1999, p. 927, courtesy of Hanna Damasio, Dornsife Imaging Center, University of Southern California).

kinds of aggression is not universally accepted). So, although patients with acquired sociopathy show some features of “developmental” psychopathy, there also seem to be distinct differences between them.

It is reported that while psychopaths score highly on both factors of the PCL-R, individuals with acquired sociopathy score highly only on Factor 2 (antisocial behavior) of the PCL-R (Broomhall, 2005) and therefore resemble individuals with an antisocial personality disorder.

Psychopathy is—among other things—related to impairments in the medial region of the orbitofrontal cortex, which is extensively interconnected with the amygdala and involved in instrumental learning and response reversal (Blair, Colledge, & Mitchell, 2001; Kiehl, Smith, Hare, & Liddle, 2000; LaPierre, Braun, & Hodgins, 1995; Mitchell, Colledge, Leonard, & Blair, 2002). In contrast, damage seen in individuals with acquired sociopathy who show reactive aggression seems to include the lateral orbitofrontal cortex (BA 47), which is said to modulate the basic brain-stream mechanisms that mediate the fight–flight response to threat (Blair, 2004).

It has been suggested that the two dimensions of aggression are genetically dissociable (Meyer-Lindenberg *et al.*, 2006). A recent neuroimaging study by Meyer-Lindenberg and colleagues (2006) reports a link between the X-linked monoaminoxidase A (MAO-A) gene and structural brain abnormalities. The MAO-A is a key enzyme in the catabolism of monoamines, especially serotonin, and is associated with impulsive aggression. In a large sample of healthy volunteers, Meyer-Lindenberg and colleagues examined the impact of a common functional

polymorphism in MAO-A on brain structure using magnetic resonance imaging (MRI). They found that the low expression variant of the MAO-A (MAOA-L), associated with an increased risk of impulsive, aggressive behavior, was linked with a significant reduction in the gray matter volume that encompasses the cingulate gyrus and the amygdala bilaterally, with a maximum volume reduction in the anterior cingulate cortex (Figure 3(A)). Additionally, there were significant reductions of gray matter volume in the insula and the hypothalamus. Moreover, there was a gender-specific (only males) increase in the lateral orbitofrontal cortex (BA 47) volume bilaterally in the low expression variant of the MAO-A as compared with the high expression variant (Figure 3(B)). Meyer-Lindenberg et al. (2006) reported the most robust structural changes in the cingulate cortex. The cingulate cortex is involved in the regulation of emotions and social behavior, a region with a very high serotonin transporter density (Mantere et al., 2002). A central serotonergic deficit is associated with impulsive aggression (Müller, 2006).

Overall, the authors argue that the MAO-A gene contributes to the reactive/impulsive dimension of aggression and not the instrumental goal-directed aggression predominantly shown by psychopaths.

## THEORETICAL MODELS OF PSYCHOPATHY

There are two main theories to explain psychopathy: the “somatic marker hypothesis” of Damasio (1994) and the “violence inhibition mechanism” model proposed by Blair (1995). The *somatic marker hypothesis* suggests that prefrontal damage leads to impaired decision-making abilities, reflecting an incapability to activate autonomic somatic states linked to the anticipation of reward and punishment. The disturbance of this “somatic marker” system leads to an insensitivity to potentially negative consequences with retained access to knowledge of social rules and potential outcomes. The neurobiological equivalent of this theory is the ventromedial prefrontal cortex (orbitofrontal and medial frontal cortex), which is assumed to be involved in cognitive processes such as decision-making.

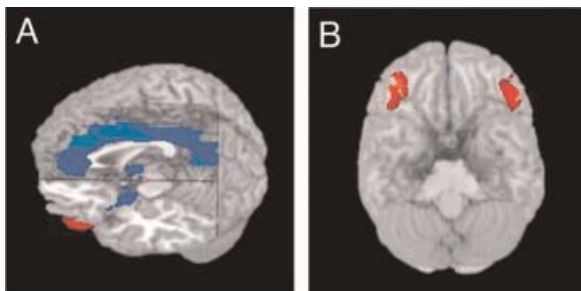


Figure 3. Limbic and paralimbic regional volume changes in MAOA-L subjects. (A) Compared with MAOA-H subjects, MAOA-L individuals showed significant volume reductions in bilateral amygdala and the cingulate cortex with a maximum in the anterior cingulate region. Male and female participants were combined. (B) Male MAOA-L individuals exhibited an increase of lateral orbitofrontal volume, bilaterally, compared with MAOA-H subjects. Females showed no effect of genotype (Meyer-Lindenberg et al., 2006, p. 6270; © (2006) National Academy of Sciences, U.S.A.).

Neuropsychological findings provide evidence for the somatic marker hypothesis and its hypothesized link between psychopathy and orbitofrontal dysfunction: For example, a study employing the Iowa gambling task (a psychological task thought to simulate real-life decision making) found that highly psychopathic subjects mimicked the gambling behavior of patients with orbitofrontal lesions (van Honk, Hermans, Putman, Montagne, & Schutter, 2002).

The *violence inhibition mechanism model* stresses the role of empathy for moral socialization. The main neurobiological equivalent of this theory is the amygdala. The model is based on the work of the ethologists Eibl-Eibesfeldt and Lorenz, who proposed that most animals have developed mechanisms for the control of aggression: submission cues displayed to a fellow aggressor to stop attacks. To give an example in humans, sad facial affects (“distress cues”) normally lead to a submission response. It is assumed that the violence inhibition mechanism is activated whenever distress cues are present and this activation is considered to cause autonomic arousal and inhibition of the on-going behavior. The dysfunction of such a mechanism may result in difficulties with empathy and in the development of psychopathy. The violence inhibition mechanism model is supported by studies showing selective impairment in the processing of sad and fearful faces in psychopathic adults (Dolan & Fullam, 2006) and children with psychopathic tendencies (Blair, Colledge, Murray, & Mitchell, 2001b).

The two theories may not be exclusive. Both somatic equivalents, the ventromedial prefrontal cortex and the amygdala, are highly interconnected. Therefore, it was suggested that psychopathy is associated with both amygdala and prefrontal dysfunctions (Mitchell *et al.*, 2006).

These two theories mentioned above help to understand the association between the neurobiological findings and psychopathy as presented below in the section on structural brain abnormalities, but certainly they are not sufficient to explain the emergence and manifestation of psychopathy. Besides the neurobiological point of view, psychosocial (e.g. poor parenting, early childhood experiences, unemployment), temperamental, and psychodynamic (e.g. “pathological narcissism”, Ronningstam & Stone, 2000) factors likely influence the manifestation of psychopathy (see also the subsection ‘Multi-Causal Model of Psychopathy’ below). A variety of psychosocial risk factors have been found for antisocial behavior and aggression, for example parenting variables including inconsistent parenting, an antisocial cultural and economic background and unemployment. According to Blair, Peschardt, Budhani, Mitchell, and Pine (2006), some social environmental variables that have an impact on antisocial behavior and aggression, such as abuse and poor parenting, have less impact on the behavior of children with emotional dysfunctions typical for psychopathy. Blair and colleagues argue that these variables have their impact through neuro-cognitive mechanisms that are dysfunctional in individuals with psychopathy. Therefore, their impact cannot be expressed. Other social environmental variables (e.g. an antisocial cultural or economic background and unemployment) are likely to have a greater influence on the behavior of children with emotional dysfunction as they influence either the motivation to offend or the child’s knowledge of antisocial strategies (Blair *et al.*, 2006).

In addition, it is noteworthy to mention that Attention-Deficit Hyperactivity Disorder (ADHD) is often a precursor of psychopathy and therefore seems to

represent another risk factor for the development of psychopathy (Thapar, van den Bree, Fowler, Langley, & Whittinger, 2006). However, the disorder of ADHD likely increases the probability, not the certainty, of psychopathic behavior.

## STRUCTURAL BRAIN ABNORMALITIES

*The frontal cortex* has been a primary target in the search for a neurobiological substrate of aggressive behavior since the case report of Phineas Gage. Many authors reported frontal lobe damage that appeared to be linked to aggressive behavior subsequently (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Blair & Cipolotti, 2000; Brower & Price, 2001; Damasio, 1994). Such cases typically involved lesions of the prefrontal, especially the orbitofrontal, cortex. For example, Blair and Cipolotti (2000) reported a case of “acquired sociopathy” as a consequence of trauma to the right frontal region, including the orbitofrontal cortex. Prefrontal volume reductions (especially of the left hemisphere) have been found in patients with temporal lobe epilepsy and a history of repeated episodes of aggressive behavior as compared with controls and with patients with temporal lobe epilepsy but without aggressive episodes (Woermann et al., 2000).

The Vietnam Head Injury Study (VHIS) yields further supportive evidence for the association between frontal lobe damage and antisocial behavior: Grafman et al. (1996) found that patients with ventromedial prefrontal head lesions demonstrated more aggressive and violent attitudes and behavior than patients with lesions in other brain regions and healthy controls. Disadvantages of this and other case reports are related to the fact that they often did not report on prior history of aggression or other known risk factors of violence. As a result, it is not clear how much of the increases in aggressive behavior can be specifically attributed to the frontal head lesions. Considering that traumatic lesions of the prefrontal cortex are often found in cases with acquired sociopathy, one may assume that psychopaths, who do not have a history of head injury, also show impairments of the prefrontal cortex but in a more subtle manner. The altered pattern of social and personal interactions in patients with frontal lobe disorders are often generalized as the “frontal lobe personality”, in which disinhibition and impulsivity dominate (also named “disinhibition syndrome”, which is characterized by impulsivity, distractibility and poor decision-making.).

Typical symptoms of psychopathy such as a lack of empathy, disturbed interpersonal relationships and instrumental aggression point towards *temporal lobe abnormalities* as a neurobiological substrate. There is widespread agreement among studies that the amygdala plays a crucial role in the emergence of aggressive behavior. Structural changes of the amygdala can both increase and decrease the probability of aggressive behavior (Blair, 2004): a decrease in aggressive behavior has been reported after bilateral amygdectomy (Ramamurthi, 1988). In addition, a severe atrophy of the amygdala was found in a sub-group of patients with temporal lobe epilepsy and aggressive behavior (van Elst, Woermann, Lemieux, Thompson, & Trimble, 2000). Furthermore, Wong, Lumsden, Fenton, and Fenwick (1994) reported in a retrospective CT study that 41% of the patients in a maximum-security mental hospital showed structural abnormalities in the temporal lobe, in particular displaying dilated temporal horn and/or reduced size of the temporal lobe.

It has also been reported that individuals suffering from a bilateral lesion of the amygdala as a consequence of encephalitis lethargica, which occurred epidemically between 1917 and 1925, showed a high probability of aggressive behavior (Garza-Trevino, 1994).

Moreover, the herpes simplex viral encephalitis is a fairly common nonepidemic encephalitis. The herpes simplex virus selectively affects the temporal and orbitofrontal regions of the brain. A high number of patients with this sort of encephalitis also show aggressive and disruptive behavior (Greer, Lyons-Crews, Mauldin, & Brown, 1989).

Finally, there is an increased frequency of psychopathic and violent behavior in well known organic brain diseases such as fronto-temporal dementia (including Pick's disease; Mendez, Chen, Shapira, & Miller, 2005), which stresses the association between fronto-temporal brain disease and psychopathic behavior.

## STRUCTURAL NEUROIMAGING STUDIES

Only a few neuroimaging studies have investigated structural brain abnormalities in individuals with psychopathic behavior (Table 1). The frontal cortex and temporo-limbic brain areas are the foci of neuroimaging research according to the two main theories of psychopathy ("somatic marker hypothesis" and "violence inhibition mechanism model"). In addition, other brain structures appear to be involved, for example, the corpus callosum.

### Frontal Cortex

Damage to the prefrontal cortex is associated with "pseudopsychopathic" behavior (acquired sociopathy). Psychopathy might be the developmental counterpart of this clinical picture. Raine, Lencz, Bihrlé, LaCasse, & Colletti (2000) assessed prefrontal gray and white matter volumes using MRI in male community volunteers with antisocial personality disorder (APD) and psychopathic-like behavior, healthy male subjects, male individuals with substance dependency, and psychiatric male controls suffering from schizophrenia-spectrum disorders, affective disorders, anxiety disorders and other personality disorders that do not fall under the category of APD. Their aim was to study brain abnormalities in non-institutionalized violent offenders. Psychopathic personality was assessed using the PCL-R as well as a history of criminal convictions. Compared with the healthy male control group, the male community volunteers with APD showed a significant reduction (11%) in prefrontal gray, but not white, matter in the frontal lobe. This deficit was visually imperceptible at a clinical radiological level. To exclude the possibility that this finding could be attributed to psychosocial risk factors, the authors also compared the male community volunteers with APD with the group of individuals with substance dependency and with a group of psychiatric patients. The APD group showed a 14% reduction in prefrontal gray matter compared with the substance-dependent group and also compared with the psychiatric control group. The authors came to the conclusion that the gray matter loss in the APD group therefore could not be attributed to psychosocial risk factors. In accordance with the

Table 1. Structural neuroimaging studies

Authors	Method	Participants	Results
Müller et al. (2007)	Voxel-based morphometry (VBM)	17 criminals with psychopathy (PCL-R* > 28), 17 non-psychopathic volunteers (PCL-R* < 10)	In comparison with the non-psychopathic volunteers criminal psychopaths showed a significant gray matter loss in the right superior temporal gyrus (STG; BA 38)
Yang et al. (2005)	MRI	16 unsuccessful (“convicted”) psychopaths (PCL-R* ≥ 23), 13 successful (“unconvicted”) psychopaths (PCL-R* ≥ 23), 23 control subjects	Negative correlation between PCL-R* score and prefrontal gray matter volume; compared with control subjects unsuccessful psychopaths (but not successful psychopaths) had a 22.3% reduction in prefrontal gray matter volume
Raine et al. (2004)	MRI	16 unsuccessful (“convicted”) psychopaths (PCL-R* ≥ 23), 12 successful (“unconvicted”) community psychopaths (PCL-R* ≥ 23), 23 control subjects	Compared with successful psychopaths and control subjects, unsuccessful psychopaths had an exaggerated structural hippocampal asymmetry (right > left) that was localized in the anterior region
Raine et al. (2003)	MRI	Community volunteers: 15 psychopathic individuals with APD** (degree of psychopathy was assessed using the PCL-R*), 25 non-psychopathic, non-APD individuals	Compared with controls, psychopathic APD** individuals showed a 22.6% increase in callosal white matter volume, a 6.9% increase in callosal length, and a 15.3% reduction in callosal thickness
Dolan, Deakin, Roberts, & Anderson (2002)	MRI	24 incarcerated individuals with personality disorders (18 psychopathic, 6 other personality disordered; assessed using the SHAPS***), 19 staff members as controls	No significant difference in frontal or temporal lobe volumes between groups
Laakso et al. (2002)	MRI	24 incarcerated males with APD** and Type 2 alcoholism (degree of psychopathy was assessed using the PCL-R*), 33 staff members and students as controls	No difference in total prefrontal, prefrontal white, or gray matter volumes when controlled for history of alcohol abuse and education
Laakso et al. (2001)	MRI	18 incarcerated male habitually violent offenders with APD** and Type 2 alcoholism (degree of psychopathy was assessed using the PCL-R*)	Negative correlation between PCL-R* scores and volume of the posterior half of the hippocampus bilaterally

*(Continues)*

Table 1. (Continued)

Authors	Method	Participants	Results
Raine et al. (2000)	MRI	21 male community volunteers with APD** (psychopathy was assessed using the PCL-R*), 34 healthy male patients, 26 male individuals with substance dependency, 21 psychiatric male controls	Compared with the healthy control group, those with APD** had a significant reduction (11%) in prefrontal gray, but not white, matter of the frontal lobe, a 13.9% reduction compared with the substance-dependent group and a 14% reduction compared with the psychiatric control group
Tiihonen et al. (2000)	MRI	28 violent offenders (13 had high scores and 15 moderate or low scores on the personality traits arrogant, deceitful interpersonal style and deficient affective experience, assessed using Hare's PCL-R*), 34 healthy men with no criminal record	Negative correlation between the right amygdala volumes and the PCL-R* ratings of the psychopathic personality traits

\*The PCL-R (Psychopathy Checklist—Revised) contains 20 items that are rated on a three-point scale. The items are summed to yield total scores, ranging from 0 to 40. The PCL-R score reflects the degree to which an individual resembles the prototypical psychopath. A score higher than 30 (respectively 28 in German-speaking countries, Müller et al., 2007; in the UK it is accepted practice to define psychopathy as a score of 25 or above, Deeley et al., 2006) supports a diagnosis of psychopathy (some authors accepted a PCL-R score  $\geq 23$  to be adequate to assign someone to psychopathy; Raine et al., 2004; Yang et al., 2005).

\*\*APD = antisocial personality disorder.

\*\*\*SHAPS = Special Hospital Assessment of Personality and Socialization (Blackburn, 1979).

somatic marker hypothesis, Raine and colleagues (2000) related the volume reductions to decision-making and learning deficiencies, characterizing individuals with APD. It must be mentioned, however, that the prefrontal cortex is a large and functionally heterogeneous region, which is composed of many cortical areas with their own distinct microstructures and connections, and the authors did not specify which sub-region (if any) was particularly reduced in volume.

Yang et al. (2005) distinguished between “successful” (psychopathic individuals with PCL-R scores  $\geq 23$ , who escaped detection for their crimes) and “unsuccessful” psychopaths (psychopathic individuals with PCL-R scores  $\geq 23$ , who were detected and convicted for their crimes) and examined whether any prefrontal structural impairment is specific to unsuccessful psychopaths as opposed to successful psychopaths. Therefore, prefrontal gray and white matter volumes were assessed using structural MRI in a sample of unsuccessful psychopaths, successful psychopaths and control subjects. Yang and colleagues found a negative association between total as well as sub-factor psychopathy scores (arrogant/deceptive, affective, and impulsive/unstable) and prefrontal gray matter volume. Unsuccessful psychopaths, but not successful ones, had a 22% reduction in prefrontal gray matter volume compared with control subjects (Figure 4). These results provide partial support for the prefrontal theory of psychopathy. Additionally, they highlight

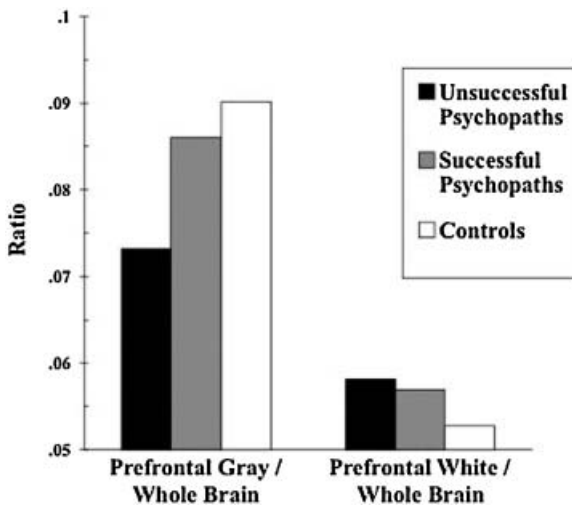


Figure 4. Prefrontal gray and white matter to whole brain ratios in unsuccessful psychopaths, successful psychopaths and healthy control subjects (Yang et al., 2005, p. 1106; © (2005) with permission from the Society of Biological Psychiatry).

that psychopathy cannot be seen as a homogeneous concept, but must be considered as a collection of different subgroups. Again, the authors unfortunately failed to specify which sub-region of the prefrontal cortex was mainly impaired in the psychopaths studied. According to the somatic marker hypothesis, psychopathy is associated with the ventromedial prefrontal cortex.

Nevertheless, the support of the somatic marker hypothesis pointing to prefrontal abnormalities is limited, since contradictory findings have also been published (Dolan et al., 2002; Laakso et al., 2002): Dolan and colleagues (2002) studied MR images of brains from two groups recruited from maximum security psychiatric hospitals. One group consisted of personality disordered offenders (18 with psychopathy and 6 with another personality disorder), and the other of staff members. The psychiatric patients were characterized using the Special Hospital Assessment of Personality and Socialization (SHAPS; Blackburn, 1979). Dolan et al. failed to find significant differences in frontal or temporal lobe volumes between the groups. Shortfalls of the studies are that (i) one quarter of the personality disordered offenders did not have a psychopathic personality, which could have reduced sensitivity in these rather small samples; (ii) the measurements did not assess gray or white matter separately, but only whole brain volume; (iii) the degree of psychopathy was not assessed using the PCL-R. The measure used to determine psychopathy in this study (SHAPS) is not consistent with Cleckley's and Hare's concept of psychopathy operationalized by the PCL-R. Hence the failure to detect structural brain abnormality in the study by Dolan et al. (2002) could be due to problems with the methods used in this study.

Total prefrontal as well as prefrontal white and cortical gray matter volumes were assessed in a group of incarcerated males with antisocial personality disorder and Type 2 alcoholism along with a group of staff members, students and their relatives (Laakso et al., 2002). Psychopathy was determined using the PCL-R. Structural MRI measurements showed smaller volumes of the cortical prefrontal regions on the

left in the APD group than in controls. Differences disappeared when data were controlled for education and duration of alcohol abuse, and there were no significant correlations between any of the measured volumes and the degree of psychopathy. Thus the observed volume deficits in the APD group seem to be more related to alcoholism or differences in education than to psychopathy.

In conclusion, there is a discrepancy between the results of Raine *et al.* (2000) as well as Yang *et al.* (2005), and the results of Laakso *et al.* (2002), who detected no differences between groups with respect to prefrontal volumes. This discrepancy could be due to putative differences in the sample of subjects studied. Whereas Raine *et al.* (2000) as well as Yang *et al.* (2005) studied community volunteers, the sample of Laakso *et al.* was restricted to violent, incarcerated offenders. In accordance with the conclusions above, this discrepancy also highlights the assumption that psychopaths cannot be seen as a homogenous group.

### **Temporo-Limbic Areas**

A few structural imaging studies reported abnormalities in the amygdala, superior temporal gyrus and hippocampus (Table 1). In a volumetric MRI study, Tiihonen and colleagues (2000) studied a group of violent offenders (13 obtained high scores and 15 moderate or low scores when tested for the personality traits of arrogance, deceitful interpersonal style, and deficient affective experience, assessed using Hare's PCL-R). They found that offenders with high scores on the psychopathic personality traits had a significant 20–21% reduction in amygdala volume on the right compared with both the moderate and low psychopathic disordered and the non-offenders after adjusting for the effects of age, intelligence, and duration of alcohol abuse. There were significant negative correlations between the right amygdala volumes and the PCL-R ratings. The authors concluded that in male offenders psychopathic personality traits are associated with amygdala volume loss.

In a recent study, Müller and colleagues (2007) assessed brain structure in psychopaths (PCL-R > 28) in comparison with non-psychopathic volunteers (PCL-R < 10) using voxel-based morphometry. Compared with non-psychopathic volunteers, the psychopaths showed a significant gray matter loss in the right superior temporal gyrus (STG; BA 38). Furthermore Müller and colleagues also found an emotion-related hypofunction in this area when studied with functional MRI. Since the right STG plays a central role in perspective awareness and empathy, the findings of Müller and colleagues support the notion that the structure and function of the right STG may be essential for the development of psychopathy.

Another structural neuroimaging study focusing on the temporo-limbic brain areas was conducted by Laakso and colleagues (2001). They studied a group of incarcerated male, habitually violent offenders with APD and Type 2 alcoholism. The authors correlated the degree of psychopathy assessed by the PCL-R with MRI-derived regional hippocampus volumes. Laakso and colleagues found a strong negative correlation between the volume of the posterior half of the hippocampus bilaterally and the psychopathy scores. This data was interpreted in the context of studies that have demonstrated the role of the hippocampus in classical conditioning and social learning. The indication is that the hippocampus may be a part of a neural circuit that predisposes psychopathic behavior. Laakso and colleagues cautioned

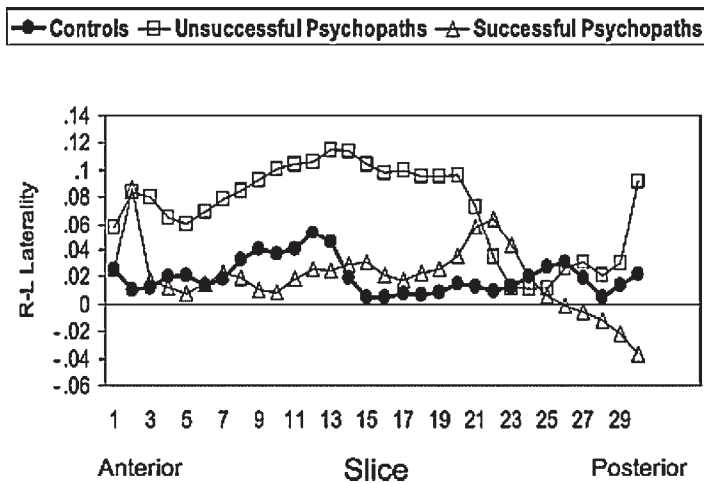


Figure 5. Right-left hippocampal laterality (R-L laterality) scores from interpolated slice volumes for the unsuccessful psychopaths, successful psychopaths and controls (Raine et al., 2004, p. 188; © (2004) with permission from the Society of Biological Psychiatry).

that their results may not be generally applicable to non-violent, non-alcoholic psychopaths.

A further structural neuroimaging study underlining the importance of the hippocampus in psychopathy was conducted by Raine and colleagues (2004), who studied unsuccessful psychopaths (“convicted”), successful (“unconvicted”) community psychopaths and control subjects. Relative to both successful psychopaths and control subjects, unsuccessful psychopaths showed an exaggerated structural asymmetry (greater right than left volume) of the anterior hippocampus (Figure 5). This result could not be explained by environmental and diagnostic confounds as demonstrated by statistical analysis. Raine et al. (2004) concluded that the anterior hippocampal asymmetry in unsuccessful psychopaths may disrupt hippocampal–prefrontal circuitry, resulting in affect dysregulation, poor contextual fear conditioning and insensitivity to cues predicting capture. The report of a relatively reduced left hippocampal structure is consistent with the finding that unpleasant emotions activate the left but not the right hippocampus (Lane et al., 1997). In line with the results reported by Yang et al. (2005), structural brain abnormalities were only apparent in unsuccessful psychopaths.

In the study by Laakso and colleagues (2001), the sample was restricted to violent, incarcerated, alcoholic offenders, who also had the diagnosis of an antisocial personality disorder (the results of Laakso and colleagues were especially confounded by the subjects’ alcoholism). Raine and colleagues (2004) studied community volunteers but both Laakso et al. (2001) and Raine et al. (2004) found hippocampal variances associated with psychopathy.

## Corpus Callosum

Other brain structures, although potentially relevant for psychopathy, have received less attention in psychopathic research so far, for example the corpus callosum. The

neurobiological basis of psychopathy appears complex, involving many brain regions, which are interconnected. It could be hypothesized, for example, that an interruption of the corpus callosum may also lead to psychopathic behavior. Raine *et al.* (2003) studied a group of psychopathic individuals with APD and a group of non-psychopathic, non-APD individuals, all from a community sample. Using MRI, they measured the white matter volume, thickness and length of the corpus callosum. They found that the psychopathic antisocial individuals had a significant 23% increase in callosal white matter volume, a 7% increase in callosal length, and a 15% reduction in callosal thickness as compared with the controls. Larger callosal volumes were associated with antisocial scores (affect and impulsive/irresponsible, but not arrogant/deceptive factors). Differences in callosal parameters were still present even after adjusting for alcohol and cannabis use, schizophrenia-spectrum disorders, head circumference and intelligence, and were independent of psychosocial deficits. The observed callosal structural abnormalities correspond with findings reporting abnormal inter-hemispheric processing phenomena in psychopathy such as reduced lateralization in P300 amplitudes (Kiehl, Hare, Liddle, & McDonald, 1999), reduced visual event-related potentials (Shumskaya, 1984), and problems in verbal dichotic listening (Raine, O'Brien, Smiley, Scerbo, & Chan, 1990).

## DISCUSSION

### Methodological Limitations

A direct comparison of structural neuroimaging studies in psychopathy is difficult due to a wide range of methodological limitations. One fundamental problem lies in the heterogeneous definition of index cases. In some cases, the psychopathic individuals had a comorbid diagnosis, for example alcoholism (Laakso *et al.*, 2001, 2002). Such comorbidity must be taken into account since drug dependence also involves widespread brain abnormalities, such as prefrontal cortex abnormalities. Furthermore, some authors studied "criminals with psychopathy" (Müller *et al.*, 2007), others studied "community psychopathic individuals with APD" (Raine *et al.*, 2000, 2003), "incarcerated personality disordered" (Dolan *et al.*, 2002), "incarcerated males with APD" (Laakso *et al.*, 2001, 2002) or "violent offenders" (Tiihonen *et al.*, 2000). As mentioned previously, there are subtle, but important, differences between individuals with the diagnosis of an antisocial personality disorder and individuals with the diagnosis of psychopathy as measured with the PCL-R; not all antisocial personality disordered individuals are psychopaths (see Figure 1).

Another major problem concerns the choice of adequate comparison groups, or the lack of adequate controls for violence risk factors. In fact, there is nearly the same inhomogeneity within control groups as found in the groups of psychopaths: some psychopaths have been compared with healthy community volunteers, others with staff members or students. To control for potential confounders, an optimal control group should be as similar as possible to the index cases (except in the distinguishing feature, namely psychopathy). Therefore, to study psychopathy, an adequate control group could consist of non-psychopathic criminals or non-psychopathic incarcer-

ated subjects. Additionally, a second control group should consist of healthy non-psychopathic controls. The controls should at least be matched in age, gender, education, ethnicity, and handedness to the index cases.

A further methodological problem lies in the varying PCL-R cut-off score. Raine et al. (2004) as well as Yang et al. (2005), who studied successful and unsuccessful psychopaths, chose a cut-off score of 23, which is lower than that of other studies and the recommended cut-off score of 30 (or of 28 in German-speaking countries; Müller et al., 2007; in the United Kingdom it is accepted practice to define psychopathy as a score of 25 or above, Deeley et al., 2006). In addition, both the studies of Raine et al. (2004) and Yang et al. (2005), showed that the group of unsuccessful psychopaths had higher PCL-R total scores (mean score 31.5, range 23–40 by Raine et al.; mean score 30.1, range 23–40 by Yang et al.) than the successful psychopaths (mean score 27.7, range 23–31 by Raine et al.; mean score 26.3, range 23–31 by Yang et al.). Therefore, it cannot be excluded that the lower PCL-R scores of the successful psychopaths are “responsible” for the failure to detect brain abnormalities in this group.

Finally, methodological divergences in data acquisition, processing and the analysis of MRI data may further contribute to differences between the studies. Considered together, these factors reduce the comparability of the studies. Furthermore, the heterogeneity and incomplete data specifications in some reported studies prevent the calculation of a meta-analysis for the comparison of the overall effects of fronto-temporal abnormalities in psychopaths with their respective non-psychopathic controls.

## Structural–Functional Brain Abnormalities in Psychopaths

Apart from methodical controversies, the studies surveyed in this review indicate that psychopathy is associated with brain abnormalities in a prefrontal–temporo-limbic system. The findings of Raine et al. (2000) and Yang et al. (2005) comply with this, since the *prefrontal (especially the orbitofrontal) cortex* is crucial in impulse control, decision-making and emotional learning, particularly in behavior adaptation to changes in reinforcement contingencies. Functional imaging studies indicate the importance of the orbitofrontal cortex in response reversal (Cools, Clark, Owen, & Robbins, 2002). In line with this, Mitchell, Colledge, Leonard, and Blair (2002) reported impaired response reversal in psychopaths.

*Temporo-limbic structures* are thought to be involved in the affective coloring of interpersonal experiences and in the development of emotional behavior regulation. The *amygdala* has been noted for its crucial involvement in the modulation and memory of emotional reactions (such as fear) and emotional learning including the formation of stimulus–reinforcement associations (Cheng, Knight, Smith, & Helmstetter, 2006). Aggleton and Mishkin (1986) called the amygdala a “sensory gateway to the emotions”. The amygdala has been linked to the emergence of psychopathy because lesions and dysfunctions of the amygdala impair aversive and appetitive classical conditioning and stimulus–reinforcement based instrumental learning (Mitchell et al., 2006) and therefore impair moral socialization. Birbaumer et al. (2005) studied fear conditioning in criminal psychopaths and healthy controls using fMRI. They demonstrated that healthy controls showed enhanced differential

activation in the limbic–prefrontal circuit (including amygdala, orbitofrontal cortex, insula and anterior cingulate cortex) during fear conditioning. The psychopaths did not activate this circuit. Although contingency and arousal ratings were normal, psychopathic individuals did not show conditioned skin conductance responses or emotional valence ratings. The authors concluded that the observed dissociation of emotional and cognitive processing may be the neural basis of the lack of anticipation of aversive events in criminal psychopaths and dysfunctional (conditioned) fear responses. While Birbaumer *et al.* (2005) found reduced amygdala activation in psychopathic individuals during aversive conditioning, Schneider *et al.* (2000) were able to demonstrate increased cortical (dorsolateral prefrontal cortex) and subcortical (amygdala) activation in antisocial personality compared with healthy controls following the acquisition phase of a differential aversive classical conditioning paradigm. The authors speculated that the increased activity in individuals with antisocial personality disorder may reflect an additional effort to form conditioned aversive reactions. The structural neuroimaging study of Tiihonen *et al.* (2000) supports the importance of the amygdala for psychopathy: Tiihonen and colleagues found a negative correlation between the right amygdala volume and the PCL-R score.

It is well known that the *hippocampus* is also implicated in contextual fear conditioning (LeDoux, 1996). The hippocampus has been shown to index familiarity, particularly to stimuli with behavioral relevance. Lesions of the hippocampus are known to impair associative learning and result in affect dysregulation, poor contextual fear conditioning, and insensitivity to cues predicting capture (Laakso *et al.*, 2001). Data showing structural abnormalities in the hippocampal region in psychopaths have been provided repeatedly by Laakso *et al.* (2001), Raine *et al.* (2004), and Ishikawa, Raine, Lencz, Bihrl, and LaCasse (2001).

Psychopaths are impaired not only in the emotional realm (Habel, Kühn, Salloum, Devos, & Schneider, 2002), but also in understanding abstract information (Kiehl *et al.*, 2004). Kiehl and colleagues reported a dysfunction of the *right anterior superior temporal gyrus* during the processing of abstract words in an fMRI study. They concluded that psychopaths may have difficulty engaging in cognitive functions that involve material without a concrete realization in the external world. The authors speculated that complex social emotions such as love, empathy, guilt, and remorse may be a form of more abstract functioning that is impaired in psychopaths. Therefore, psychopaths cannot rely on such abstract functions and fail to modulate their behavior accordingly. The crucial role of the superior temporal gyrus (STG) in mediating psychopathic behavior is further supported by data of Müller *et al.* (2007), who showed a significant gray matter loss in the right superior temporal gyrus in criminal psychopaths using structural MRI (Table 1). The authors interpreted their findings with respect to the lack of empathy in psychopaths because the right STG plays a central role in perspective awareness and empathy. In the same study, Müller and colleagues supported their structural findings by additionally using fMRI, in which they found an emotion-related hypofunction in the right STG.

So far, we have reviewed the findings that psychopaths showed deficits in frontal and temporal as well as subcortical limbic structures. All these structures are highly interconnected. For this reason, the *corpus callosum* also seems to play a role in the

emergence of psychopathy. In a functional study of murderers pleading not guilty by reason of insanity, Raine, Buchsbaum, and LaCasse (1997) reported, among other things, reduced glucose metabolism in the corpus callosum, indicating that the corpus callosum might contribute to violent behavior (at least in the case of murderers pleading not guilty by reason of insanity). In addition, Raine et al. (2003) showed that psychopathic individuals had an increase in callosal white matter volume (Table 1), and they found increased functional interhemispheric connectivity. Functional interhemispheric connectivity was assessed using a consonant–vowel–consonant trigram identification task (either presented in the left or the right visual field, or both simultaneously) and a letter-matching task (upper case and lower case letters that either matched or did not match were presented either within or between visual fields). The greater interhemispheric connectivity could account for the common observation of reduced lateralization in P300 amplitudes in psychopaths (Kiehl et al., 1999).

The results presented indicate that psychopathy cannot be explained by one particular neurobiological theory or by one neurobiological substrate alone. Rather, the various brain abnormalities seem to involve a network, including prefrontal regions as well as temporo-limbic areas.

Because the ventromedial prefrontal cortex and the limbic structures are closely interconnected, it is possible that pathology in one of these regions will result in abnormalities in the other. This assumption can be drawn on the basis of the observation that measures that are thought to require amygdala involvement are substantially impaired in adults with psychopathy and children with psychopathic tendencies, whereas performance on tasks thought to require the orbitofrontal cortex is substantially impaired only in adults (Blair et al., 2001a). This finding could reflect the developmental course of psychopathy, assuming that first there are abnormalities in limbic structures, which, in the long run, also result in orbitofrontal impairments; due to interconnectivity, a reduction in afferent input from the limbic structures may have a negative impact on the functionality of the orbitofrontal cortex (Blair et al., 2001a). On the other hand, this could reflect the lifestyle of psychopaths: Because psychopathy is sometimes associated with substance abuse (e.g. in consequence of their sensation-seeking behavior), this could produce additional orbitofrontal impairments (Blair et al., 2001a).

To summarize, there are too few structural neuroimaging studies to date (and many of them come from the same research group) to draw definite conclusions. The existing body of evidence tentatively supports the idea that psychopathy is associated with brain abnormalities in a prefrontal–temporo-limbic circuit—regions that are involved in emotional and learning processes (Figure 6). It should be mentioned here that these brain regions are also found to be impaired in patients with other mental disorders such as schizophrenia, who also show deficits in impulse control and emotional information processing (e.g. face processing) (Gur et al., 2002; Kiehl et al., 2000; Schneider et al., 2006). Therefore, these brain regions seem to be relatively unspecific for psychopathy itself. To study which structural and functional brain abnormalities are in fact specific to psychopaths and the differential meaning of these brain regions for psychopathy in comparison with other mental disorders, one possible topic of future research could be to compare psychopaths with individuals suffering from other mental disorders that display similar brain abnormalities, for example schizophrenic patients.

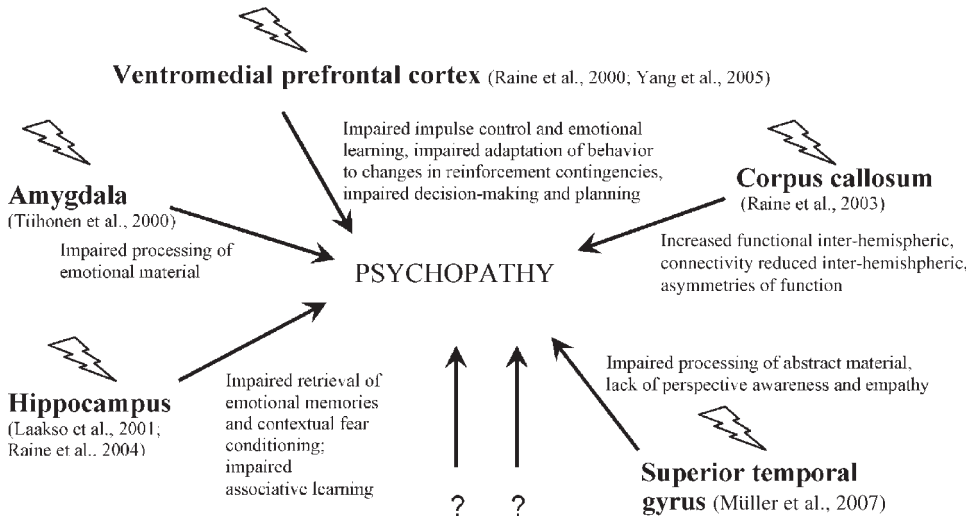


Figure 6. Affected brain regions in psychopathy (findings of the reviewed structural neuroimaging studies).

### Successful and Unsuccessful Psychopaths

It is noteworthy that Yang *et al.* (2005) as well as Raine *et al.* (2004), who distinguished between successful and unsuccessful psychopaths, found brain abnormalities (hippocampal and prefrontal) only in unsuccessful psychopaths. This is in line with a previous report from this research group on this sample of psychopaths: Ishikawa *et al.* (2001) reported that unsuccessful psychopaths had reduced autonomic stress reactivity and executive function deficits (measured with the Wisconsin Card Sorting Test) compared with controls, while successful psychopaths had heightened autonomic stress reactivity and better executive functioning. It is known that reduced autonomic and executive functioning is associated with structural damage of the prefrontal cortex (Damasio, 1994). Hence Yang and colleagues explained their discovery of reduced prefrontal volume in unsuccessful psychopaths with reference to the somatic marker hypothesis, which states that intact prefrontal and autonomic functioning allows an individual to process cues in risky situations and make appropriate decisions. Successful psychopaths who seem to have intact functioning may be more able to avoid conviction. In contrast, unsuccessful psychopaths, who lacked enhanced decision-making skills during their criminal acts, may be more prone to detection and conviction. It should be noted, however, that the somatic marker hypothesis focuses on the ventromedial prefrontal cortex, whereas the Wisconsin Card Sorting Test (WCST) is associated with activation primarily of the dorsolateral prefrontal cortex (Bechara, Tranel, & Damasio, 2000).

As the hippocampus is involved in contextual fear conditioning, Raine *et al.* (2004) argued that, due to hippocampal impairments, unsuccessful psychopaths might become insensitive to cues that predict punishment and capture and therefore be prone to capture and conviction.

The discrepancies between successful and unsuccessful psychopaths indicate that psychopathy is not a uniform concept. Furthermore, the concept of Hare's

psychopath itself also includes two factors, emotional detachment and antisocial behavior, which can vary considerably between psychopaths and may have different behavioral as well as neural implications, leading however to the same general psychopathy score. Nevertheless, Hare's concept of psychopathy is not restricted to individuals showing criminal or deviant behavior, but also includes socially well adjusted and successful psychopaths. Therefore, the failure to find a prefrontal and hippocampal brain abnormality in successful psychopaths may indicate that a deficit in prefrontal-hippocampal circuitry, at least on a structural level, may not be a primary pathology and core characteristic of the concept of psychopathy itself.

As mentioned above, the reported discrepancies could also reflect a methodological problem, since in the studies of Ishikawa et al. (2001), Raine et al. (2004) and Yang et al. (2005) the PCL-R cut-off was somewhat lower than in other studies and the group of unsuccessful psychopaths had higher PCL-R total scores than the successful ones.

### **Multi-Causal Model of Psychopathy**

The documented brain abnormalities are not sufficient to explain the emergence of psychopathy. As mentioned above, "psychopathy" may result from the interaction of various factors and is probably best explained by a vulnerability stress model or a bio-psycho-social approach. Experiences during the formative years and socialization as well as neurobiological and genetic endowment interact with the emergence of psychopathy. The bio-psycho-social approach of Paris (1993) tries to include the present evidence for biological, psychological and social factors in the development of personality disorders. According to this model, biological factors determine underlying temperamental characteristics in an individual, who will—under certain additional psychosocial risk factors—develop a personality disorder.

While psychosocial risk factors are well investigated, neurobiological factors, and their interaction with psychosocial factors, remain poorly understood. A first clear link between genetic predisposition and impulsive aggression has been provided for the monoaminoxidase A (MAO-A) gene (Meyer-Lindenberg et al., 2006). This link does not hold true, unfortunately, for instrumental aggression, primarily seen in psychopaths.

### **Implications for Forensic Psychiatry**

The increasing identification of neurobiological aspects of psychopathy is of high relevance for forensic psychiatry, especially with respect to appropriate programs for the management of individuals with psychopathy. Neurobiological approaches could offer a great potential for the establishment of adequate prevention and treatment programs. Furthermore, the increasing number of neurobiological findings raises questions regarding legal responsibility in psychopathy (Herpertz & Saß, 2000). In addition, against the background of the increasing frequency of psychopathic and aggressive behavior in well known organic brain diseases affecting frontal and temporo-limbic areas such as fronto-temporal dementia, herpes simplex and rabies encephalitis, and temporal lobe epilepsy, for example, brain imaging methods should be applied by default or at least much more often in individuals with psychopathic behavior or violent offenders to exclude organic brain diseases. To date, this is not generally established as a standard in forensic practice.

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