Neurobiology of borderline personality disorder (BPD) and antisocial personality disorder (APD)

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Summary

Affective disorders and personality disorders are associated with a combination of (1.) genetic polymorphisms predominantly affecting the serotonin system and the HPA (stress) axis, (2.) deficits in brain development, (3.) early adverse (traumatising) childhood experiences and (4.) later (adolescent) adverse experiences. Neurobiological studies have revealed structural and functional deficits especially in limbic and paralimbic brain areas, as well as their interaction between each other and interactions with cognitive-executive brain regions. On the basis of this general assumption, the following review is about experimental-empirical studies concerning the possible neurobiological background of personality disorders, particularly borderline personality disorder (BPD) and antisocial personality disorder (APD)/psychopathy (PP).

Key words: personality disorders; neuroscience; fMRT; EEG; early trauma; emotion regulation; impulse control

Borderline personality disorders

Structural imaging

Meta-analysis have revealed reduced hippocampal and amygdalar volumes in borderline personality disorder (BPD) patients compared to healthy controls [1, 2]. Both brain areas are associated with affect regulation and emotion. For that reason, the volume reduction may be a biological substrate of BPD symptomatology [3]. However, hippocampal anomalies are not specific to BPD; for example, patients with post-traumatic stress disorder (PTSD) have also shown reduced volumes [4, 5]. The influence of traumatic experiences on neurobiological anomalies in BPD is not yet clear: Driessen et al. [6] found reduced hippocampal volumes as well as a non-significant trend for reduced amygdala volumes in a sample of BPD patients with a history of physical or sexual abuse in childhood [6]. The comparison of BPD patients with co-morbid PTSD and BPD patients without PTSD showed that the traumatic events were related to reduced hippocampal volumes [7, 8]. The results of a recent meta-analysis suggest that hippocampal volumes are diminished in patients with BPD relative to controls especially in cases with a co-morbid PTSD [9]. In addition, left hippocampal volume was inversely correlated with a lifetime history of aggressive behaviour [10]. The reduction was more pronounced in patients with multiple hospitalisations [10]. This finding seems to be important because the hippocampus has demonstrated to be one important brain region for the control of aggression and impulsive behaviour. The authors concluded that their findings suggest that structural changes might facilitate aggressive behaviour [10].

Apart from structural abnormalities in the amygdala and the hippocampus, reduced volumes have been found in frontal regions [11], for example in the orbitofrontal and ventromedial prefrontal cortex (OFc, VMpFC), the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC; [12]), in the superior parietal cortex and the precuneus [13]. In BPD subjects with the co-morbid diagnosis of dissociative amnesia or dissociative identity disorder, the left post-central gyrus was significantly increased compared to controls and to BPD subjects without these symptoms [13]. In a study examining teenagers with a first presentation of BDP compared to controls, deficits in the OFC, but not in the hippocampus or amygdala were identified [14]. The orbitofrontal cortex is involved in the conscious perception of emotions, the emotional preparation and motivation of actions, the assessment of consequences of one’s own behaviour and of individual and social risks, the identification of the emotional expression and of the meaning of the actions of other people (empathy), as well as learning and control of socially adequate behaviour. Hippocampal and amygdala volume reductions observed in adult BPD samples may develop during the course of the disorder, although longitudinal studies are needed to examine this.

Minzberg and colleagues [15] demonstrated an increased grey matter concentration in the amygdala and a decreased concentration in the rostral/subgenual ACC compared to healthy subjects. Others suggested a potential association between 5-HT1A receptor gene polymorphism and amygdala volume. This finding might be disease-related and could contribute to the amygdala findings [16]. Soloff and colleagues [17] demonstrated that BPD suicide attempters had
One characteristic feature of BPD is self-injurious behaviour. High-lethality attempters demonstrated decreases in the right OFC, the right mid-superior temporal gyrus, the right insula and the right parahippocampal gyrus. The results indicated structural differences with respect to suicidal behaviour.

The studies mentioned above suggest that BPD is associated with abnormalities in the limbic structures and that these abnormalities probably underlie emotional dysfunction in BPD symptomatology. Decreased volumes of these limbic structures are suggested to hold promise as candidate endophenotypes in BPD [2].

Functional neuroimaging

Pain

One characteristic feature of BPD is self-injurious behaviour in conjunction with a reduced pain perception. Female inpatients with BPD who do not report pain during self-injury (BPD-nP) showed less pain intensity during the cold pressure test compared to BPD patients who report pain during self-injury (BPD-P), female inpatients with major depression, and also compared to healthy subjects. In addition, the total absolute theta power was significantly higher in the BPD-nP group compared to depressive patients and healthy subjects, with a trend toward being significantly higher compared to the BPD-P group. It is suggested that increased theta activity is characteristic of this group of patients and may be indicative of diffuse brain dysfunction [18].

Schmahl et al. [19] examined nociceptive processes in patients with BPD using event-related potentials (ERPs): ERPs of BPD patients differed only marginally when compared to those of healthy controls. However, BPD patients showed significantly higher heat pain thresholds and lower pain ratings than control subjects despite similar electrophysiological responses. This probably indicates that the sensory-discriminative pain processing does not differ between groups. Hypoalgesia in BPD may be influenced by altered intracortical processing or active suppression of pain. Schmahl et al. demonstrated smaller overall volumes of activity in BPD patients than in controls in response to identical heat stimuli. When the temperature was adjusted according to the pain threshold, BPD patients showed increased responses in the DLPFC and decreased activity in the perigenual ACC and the amygdala compared to healthy controls. The authors assumed that the interaction between DLPFC, ACC, and amygdala is associated with an anti-nociceptive mechanism [20].

Vigilance and resting state

An examination of EEG-vigilance (arousal, wakefulness) in patients with BPD showed significantly lower rates of EEG-vigilance compared to obsessive compulsive disorder (OCD) patients. The result may indicate an instable regulation of EEG-vigilance in BPD patients and is in line with the assumption that sensation seeking and impulsivity in BPD have a compensatory and autoregulatory function to stabilise the activation of the brain [21].

Studies using [19F]-fluorodesoxyglucose positron emission tomography (FDG-PET) found differences in the prefrontal cortex of patients with BPD compared to healthy controls during resting conditions [22]. However, the results are inconsistent: Juengling et al. [23] demonstrated a hypometabolism in the left hippocampus and an inCREASEd metabolism in the ACC, the superior frontal gyrus, the right inferior frontal gyrus, and the right precentral gyrus in patients with BPD. By contrast, a decreased metabolism in the ACC, the DLPFC, and the basal ganglia was revealed in patients compared to controls [24]. De la Fuente and colleagues demonstrated a relative hypometabolism in prefrontal areas, the anterior part of the cingulate cortex as well as thalamic, caudate, and lenticular nuclei [25].

Proton magnetic resonance spectroscopy ([1H]MRS) studies also provide an insight into baseline neuronal function by measuring levels of metabolite concentration. Van Elst et al. [26] conducted a pilot study assessing the N-acetylaspartate (NAA) concentration (a marker of neuronal integrity) in patients with BPD and no comorbid psychiatric illnesses versus normal controls. The results indicated a significant reduction in NAA concentration in the DLPFC of BPD patients compared to normal controls, which would indicate deficits in executive function, working memory, or the ability to integrate emotion and cognition. Soloff et al. [27] used FDG-PET imaging procedures to assess serotonergic functioning. The results suggest that, compared to controls, BPD patients showed diminished glucose intake in orbital and medial regions of the prefrontal cortex. This finding is noteworthy when considering that BPD participants were not depressed, which provides the preliminary evidence that serotonergic dysfunction in BPD is not solely the result of co-morbid major depression.

Presentation of emotional stimuli

Neuroimaging studies showed that a network of regions is involved in emotion regulation, including the amygdala, hippocampus, and the orbitofrontal-ventromedial frontal cortex. The crucial function of these brain regions in the expression, control, and modulation of emotion and impulsivity in humans has led to the hypothesis that dysfunctions in these regions could be the reason for some of the psychopathological symptoms seen in BPD.

In general, neuroimaging provides evidence for a heightened responsivity to emotional stimuli among individuals with BPD. A greater activation of the amygdala in response to the negative compared to the neutral stimuli was reported in BPD patients, who met the affective instability criterion for BPD, had no current Axis I disorder, and were medication-free compared to healthy controls. However, the two groups did not differ in their self-reported emotional response to the stimuli suggesting that the BPD group did not experience the pictures to be more arousing or more negative [28]. In addition, the frequency of negative stimuli seemed to have an important influence on neurobiological findings: BPD patients showed greater amygdala activation than healthy controls and patients with schizotypal personality disorder, and a prolonged return to baseline, particularly at repeated presentation of emotional pictures [29].

Other research has demonstrated that BPD patients with co-occurring Axis I disorder showed higher levels of left amygdala activation at the presentation of sad, neutral, and
fearful faces [30]. Interestingly, the most striking difference between the groups occurred in response to neutral items: the evaluation of these pictures was uniformly negative, threatening, and untrustworthy. The findings from this study provide a foundation for elucidating the neuronal substrates of behavioural and emotional facets of BPD, contributing to disturbed interpersonal relationships [30].

Another study focusing on emotions like fear and anger in BPD showed a significantly larger deactivation in the bilateral rostral/subgenual ACC to fear in patients compared to controls. However, there were no significant differences between groups in these areas in response to anger. The authors concluded that BPD patients exhibit changes in fronto-limbic activity in the processing of fear stimuli, with an exaggerated amygdala response and an impaired emotion-modulation of ACC activity. The relative hypo-responsivity to anger compared to fear could be related to an inability of BPD patients to manage socially undesirable behaviour in interpersonal settings [31]. Hypervigilance and emotional dysregulation may influence disturbed interpersonal relationships [30]. In addition, the presentation of fear stimuli seemed to be related to a dysfunctional fronto-limbic connectivity in BPD patients during fear processing with reduced connections to the frontal areas to overt fear processing and reduced connections to the thalamus for automatic fear processing [32]. In addition, prolonged amygdala responses and medial prefrontal dysfunctions have been demonstrated during instructed fear processing in BPD patients: patients showed increased connectivity between the amygdala and the ventromedial prefrontal cortex (VMPFC) and decreased connectivity of the subgenual ACC with the dorsal ACC [33].

The presentation of autobiographical memories led to increased BOLD responses in the bilateral OFC and insular cortex, left ACC, and medial prefrontal cortex as well as in the parietal and parahippocampal areas; these results were related with a more aversive and arousing experience assessed by self-reports [34]. In addition, hyperactivations were seen during neutral and negative stimuli. The authors concluded that the lack of selective activation of areas involved in autobiographical memory retrieval suggests a general tendency towards a self-referential mode of information processing in BPD or a failure to switch between emotionally salient and neutral stimuli [34].

**Traumatic experiences or PTSD diagnosis** seem to influence the processing of emotions. The presentation of traumatic memories and aversive, but non-traumatic memories in patients with BPD led to the activation of different neural networks: BPD patients without PTSD revealed predominantly increased BOLD responses in the OFC and the Broca area, whereas patients with PTSD showed increased responses in the amygdala, anterior temporal lobes, and mesio-temporal areas [35]. Beblo et al. [36] investigated neural correlates of the recall of unresolved life events in patients with BPD and healthy controls. Individual cue words were used in order to stimulate autobiographical memories. When contrasting unresolved and resolved life events, patients showed significant bilateral activation of fronto-temporal areas including the insula, amygdala, left posterior cingulate cortex, right occipital cortex, and cerebellum. The authors concluded that the activation of both amygdala and prefrontal areas could reflect an increased effortful but insufficient attempt to control intense emotions during the recall of unresolved life events in patients with BPD.

Buchheim and colleagues [37] examined the functional neuroanatomy of attachment trauma while BPD patients were telling individual stories to attachment relevant picture stimuli (Adult Attachment Projective [38]). BPD patients and healthy controls told stories in response to the AAP pictures while being scanned. Group differences in narrative and neural responses to “monadic” pictures (characters facing attachment threats alone) and “dyadic” pictures (interaction between characters in an attachment context) were analysed. Behavioural narrative data showed that monadic pictures were significantly more traumatic for BPD patients than for controls. In addition, BPD patients exhibited significantly more anterior mid-cingulate cortex activation in response to monadic pictures than controls. In response to dyadic pictures patients showed more activation in the right superior temporal sulcus and less activation in the right parahippocampal gyrus compared to controls. These results give evidence for potential neuronal mechanisms of attachment trauma underlying interpersonal symptoms of BPD, such as fearful and painful intolerance of aloneness and reduced positive memories of dyadic interactions [37].

In summary, emotion processes and their neurobiological bases are deficient in BPD patients; for example, amygdala responses are prolonged and enhanced especially during repeated presentation of emotional stimuli. In addition, traumatic experiences play an important role in these processes. These deficits may be part of the neural mechanisms underlying emotional dysregulation in BPD patients [33]. Functional anomalies could also influence cognitive processes. A recent study by Enzi and colleagues [39] demonstrated that deficient emotion processing is likely to affect the reward system in patients with BPD.

**Executive functions**

BPD patients often have deficits in executive processes, for example flexibility, inhibitory control, planning, and error processing. Electrophysiologically, diminished error-related responses and inhibition-associated potentials were demonstrated in patients compared to healthy subjects [40, 41]. These responses were influenced by the impulsiveness of BPD patients. The assessment of decision-making and reward processes demonstrated that patients with BPD made more risky choices which did not improve their performance during the Iowa Gambling Task [42]. Concerning electrophysiological responses, feedback-related negativity was diminished and was correlated with enhanced impulsivity and enhanced risk taking behaviour in patients. In contrast, P300 amplitudes following negative feedback were increased in BPD patients. These findings suggest dysfunctional decision-making processes in patients and especially problems with learning to avoid disadvantageous choices [42]. Functional MRI studies focusing on the inhibition of behavioural responses demonstrated that patients with impulsive personality disorders (BPD; antisocial personality disorder)
exhibited more widespread activity with bilateral activation in the medial frontal gyrus, the superior frontal gyrus, and the inferior frontal gyrus as well as the ACC. The authors suggested inefficient processing with activations in a wider cortical area compared to healthy subjects [43].

Other studies focused on the influence of emotions on cognitive processes. The interaction of negative emotions and behavioural inhibition led to decreased responses in the VMPFC (e.g., OFC, subgenual ACC) and extended amygdalar-ventrostriatal activity [44]. The authors assumed that their findings suggested specific fronto-limbic neuronal substrates associated with core clinical features of emotional and behavioural dyscontrol in BPD [44]. In addition, hyper-responsiveness to distracting emotional pictures negatively affected the working memory performance of patients [45].

Summary

The cause of borderline personality disorder is complex, with several factors interacting in various ways with each other. It is a complex dynamic system both psychologically and neurobiologically. Genetic factors and adverse childhood experiences (e.g., attachment trauma, emotional neglect) may cause emotional dysregulation and heightened impulsivity leading to dysfunctional behaviours and psychosocial deficits, which again could reinforce emotional dysregulation and impulsivity. Structural and functional neuroimaging have revealed a dysfunctional frontolimbic network of brain regions, which seem to mediate BPD symptomatology. Taken together, these findings may suggest that BPD patients exhibit reduced hippocampal, orbitofrontal, and amygdala volumes and an increased activation in the amygdala in response to negative emotional stimuli. However, some neuroimaging studies also showed inconsistent results; the impact of various influencing factors on neurobiological correlates of BPD should be investigated in more detail.

Neurobiological basis of antisocial personality disorder (APD) and psychopathy

There is no universally accepted definition of personality disorders related to antisocial behaviour. A frequently used definition is given in DSM-IV as “Personality disorders cluster B” with the following diagnostic criteria: (1.) Failure to conform to social norms with respect to lawful behaviours as indicated by repeatedly performing acts leading to arrest; (2.) deceitfulness, as indicated by repeatedly lying, use of aliases, or conning others for personal profit or pleasure; (3.) impulsivity or failure to plan ahead; (4.) irritability and aggressiveness, as indicated by repeated physical fights or assaults; (5.) reckless disregard for safety of self or others; (6.) consistent irresponsibility, as indicated by repeated failure to sustain consistent work behaviour or honour financial obligations; (7.) lack of remorse, as indicated by being indifferent to or rationalising following having hurt, mistreated, or stolen from another individual. The World Health Organisation’s International Statistical Classification of Diseases and Related Health Problems, tenth edition (ICD-10), defines a conceptually similar disorder to antisocial personality disorder called (F60.2) dissociative personality disorder. Psychopathy can be defined for example by “Hare’s Psychopathy Check List-Revised” (PCL-R; [46]): (1.) Aggressive narcissism: for example glibness/superficial charm, grandiose sense of self-worth, pathological lying, lack of guilt, lack of empathy; (2.) Socially deviant lifestyle: for example need for stimulation, parasitic lifestyle, poor behavioural control, lack of realistic, long-term goals, juvenile delinquency.

Functional neuroimaging

Impulsive aggression

Reactive-impulsive aggression and violence are the dominant types of antisocial behaviour and are positively correlated to increased levels of anger and impulsivity. They occur as a reaction to perceived threats or provocation and are often followed by remorse [47]. Signs of a relationship between impulsive aggression and a reduced volume of the frontal lobe or other dysfunctions of the prefrontal cortex, especially OFC and VMPFC, are found in patients with a variety of psychiatric disorders such as BPD [48] and APD [49, 50], in suicidal behaviour [51], and in murderers pleading not guilty by reason of insanity [52, 53]. One major function ascribed to VMPFC and OFC is the regulation of emotional responses, especially in the context of threatening and risky situations.

OFC and VMPFC are closely interconnected with other limbic brain areas such as the rostral ACC and the amygdala [54]. Accordingly, the relative balance of activity between the prefrontal cortex and limbic structures could be disturbed, when it comes to impulsive aggression and violence [55]. Raine et al. [52] demonstrated reduced prefrontal and increased subcortical activity, specifically in murderers who committed their violent acts in an unplanned and impulsive manner. Patients with impulsive aggression showed an exaggerated amygdala activity and reduced OFC activation in response to angry faces, providing evidence for an amygdala-OFCC dysfunction in response to social threat signals in individuals with impulsive aggression [47]. These data suggest a link between a disturbed frontal-limbic circuitry and a state of sub-cortical hyper-arousal (primarily mediated by the amygdala) leading to impulsive aggression and emotional dysregulation. The amygdala and the OFC are key structures in the so-called ventral system of emotion perception [56]. According to this concept, the ventral system is important, among others, for the rapid appraisal of emotional material and the automatic regulation of autonomic responses to emotional stimuli. It is assumed that activation of the dorsal ACC and of the OFC/VMPFC in healthy impulsive individuals operates as a compensatory mechanism, which is absent in clinical populations [57]. Patients with conduct disorder and APD, likewise characterised by heightened impulsivity, showed a marked decrease in the dorsal ACC when viewing negative pictures [57, 58]. In conclusion, prefrontal hypofunction in combination with amygdalar hyperfunction consistently occur throughout anatomical and functional studies with clinical and forensic populations, which are characterised by emotional dyscontrol and impulsivity/aggression.
Proactive-instrumental aggression and psychopathy

Persons satisfying the criteria of psychopathy are characterised by a dominance of instrumental, proactive, premeditated or “predatory” aggression in terms of goal-directed activity. Psychopaths often exhibit a high degree of self-control at lying, deceiving and manipulating others, and simulating empathy for example, while hiding their true motives. Psychopathy is considered a reliable predictor for violence, high rates of recidivism, and poor treatment responsivity [59].

A thinner cortex in a number of areas has been demonstrated in psychopathic inmates compared to non-psychopaths, for example in the left insula, the dorsal ACC, the precentral gyri, and the anterior temporal cortices [60]. In addition, the connectivity between dorsal ACC and insula was decreased. A study comprising a large sample of incarcerated men demonstrated decreased grey matter in several limbic and paralimbic areas, such as parahippocampal areas, amygdala and hippocampal regions, temporal pole, posterior cingulate, and OFC [61]. Actual studies focusing on brain connectivity by means of diffusion tensor imaging extended these findings by demonstrating that psychopathy is associated with a reduction of functional connectivity between the ventromedial prefrontal cortex (VMPFC) and the amygdala as well as between VMPFC and the medial parietal cortex [62, 63].

In adult psychopaths a combined amygdala-OFC dysfunction can be found [62, 63]; they particularly show deficits in associative learning and emotionality [64–66]. Regrettably, neuroimaging data on amygdala and OFC activation in psychopaths are somewhat inconsistent: some studies reported reduced activation of limbic areas in psychopaths compared to controls using aversive conditioning [67, 68] or affective memory tasks [68], whereas others found enhanced activations in the amygdala, the OFC, and the dLPPC during emotional learning [69, 70] and the processing of negative emotional pictures [71]. Using a facial emotion processing task, Decleyn et al. [2006] failed to detect any amygdala or OFC activity in criminal psychopaths [72]. Possible reasons for these discrepancies are different stimulation paradigms across studies, small sample sizes, and differences regarding the symptomatology. Another possibility is that these differences are due to differences in the serotoninergic control of the VMPFC via 5HT_2a receptors: an increase in density and affinity of these receptors leads to an increased activation of the VMPFC and reduced levels of impulsivity, while a decrease in density and affinity of 5-HT_2a receptors leads to a decreased VMPFC activity and higher impulsivity [73, 74]. These findings point to the existence of subtypes of psychopathy, including impulsive and non-impulsive ones depending on the strength and the moment of psychotraumatization.

A lack of empathy has often been assumed in the context of both reactive and proactive psychopathic aggression and violence. A study concerning empathic and violent behaviour in healthy subjects by varying the appropriateness of empathic/aggressive behaviour showed identical activations in a circuit including the VMPFC and the amygdala for the appropriate situations, irrespective of whether the behaviour was violent or compassionate. This finding suggests that context-appropriate behaviour is guided by a common neural system [75]. Others demonstrated a participation of the dorsomedial PFC in cognitive aspects of social interaction, while the OFC/VMPFC is involved in affective processes associated with compassion for the suffering opponent [76]. Interestingly, stronger OFC/VMPFC activations for more empathic participants and a positive correlation between amygdala activity and pain of the opponent were reported. These findings point towards a higher responsiveness of the OFC/VMPFC to distress cues signalled by the amygdala in more empathic individuals and may relate to a neuronal basis of empathy deficits as seen in psychopaths.

The investigation of a possible link between affective and cognitive processes in psychopathy revealed that, unlike healthy subjects, persons with dissocial personality disorder did not show any influence of negative conditions on behavioural results; in psychopaths negative emotions did not disturb cognitive tasks [77]. In addition, psychopaths exhibited a reduced activity in the superior temporal gyrus (STG) as opposed to an increase in controls at presentation of negative emotional stimuli. This is in line with other studies showing increased temporo-parietal activity and decreased prefrontal activity at the presentation of incompatible material in healthy subjects and reflecting a “load” of more challenging cognitive processes [78]. According to the authors, this indicates that the interaction between STG and the VMPFC is disturbed in psychopaths.

Fecteau et al. [79] tried to distinguish between the recognition of pain of others and caring for it in a sample of persons with psychopathic personality traits in a non-psychiatric sample. The observation of painful stimuli led to a significant reduction in the amplitude of TMS-induced motor evoked potentials. Individuals with the greatest MEP reduction were those scoring highest on the cold-heartedness measure. This could indicate that psychopathic patients can have a better understanding of the suffering of others, but also that they have no concern for the pain of others. This coincides with findings of spared mental abilities in psychopaths [80].

In summary, the neurobiological findings on psychopathy suggest that the condition is due to dysfunctions of the ventral and ventromedial prefrontal regions, insular cortex, temporo-parietal cortical areas, subcortical limbic regions, and in particular the amygdala. According to Yang and Raine [81], core psychopathy deficits impair (1.) the evaluation of positive or negative reinforcers (OFC/VMPFC), (2.) the processing of affective stimuli including its context (amygdala, hippocampus), (3.) the assessment of emotional salience and regulation of emotional responses (ACC), and (4.) the pain and empathy system (insula, STG).

Subtypes of psychopathy

Successful versus unsuccessful psychopaths

The general assumption that psychopathy is characterised by a hyporesponsibility of the autonomic stress response has been questioned by studies on distinct subgroups of criminal psychopaths, who have been either convicted for their crimes (unsuccessful psychopaths) or have remained undiscovered so far (successful psychopaths). Unsuccessful psychopaths showed reduced cardiovascular stress reactivity, which is in line with previous research. However, successful
psychopaths demonstrated even greater autonomic reactivity and stronger executive functions than both the unsuccessful psychopaths and the controls [82]. Another study with the same sample of psychopaths demonstrated a reduction in prefrontal grey matter volumes specific to the unsuccessful psychopaths compared with control subjects and successful psychopaths [83]. Decreased prefrontal volumes may render unsuccessful psychopaths particularly susceptible to poor decision-making, impulsive aggression, and unregulated antisocial behaviour – thus raising the probability of ‘getting caught’. By contrast, successful psychopaths showed a relative sparing of prefrontal grey matter that may provide them with normal executive functioning and intact capacities for the control of affective states. This could allow successful psychopaths to react sensitively to environmental cues signalling danger and, therefore, to avoid conviction [82, 83]. A number of recent studies confirmed that successful psychopaths exhibit normal cognitive abilities related to normal structure and functions of the dorsolateral PFC and dorsal anterior cingulate cortex [84]. Accordingly, they reveal an intact P300 component of the event-related potential in cognitive tasks, while their ventral and ventromedial frontal cortex mostly reveals a hyporesponsivity [85].

Primary and secondary psychopaths
A related distinction between subtypes of psychopathy is that between “primary” or “low-anxious” and non-impulsive psychopaths on the one hand, and “secondary” or “high-anxious” and impulsive ones on the other. The study by Motzkin et al. [63] on prefrontal connectivity in psychopathy revealed that low-anxious, primary psychopaths reveal a significantly higher connectivity between VMPFC and amygdala compared to secondary psychopaths with relatively low connectivity resulting in lower or higher levels of impulsivity, respectively. While psychopaths are generally characterised by an inter-hemispheric imbalance, those belonging to the primary, impulse-controlled subtype revealed a hypoactive right (mostly frontal) hemisphere, while those included in the secondary, impulse-driven subtype were characterised by a hyperactive left hemisphere (overview in [86]).

Neuropsychological and genetic deficits in individuals with APD
Increased impulsivity and impulsive aggression have long been associated with a central serotonin deficit both in healthy subjects as well as in various clinical populations [87–90]. Furthermore, there are a number of studies describing a reduced serotonergic modulation of frontal brain areas in the context of impulsivity and aggression [48, 91]. These studies provide neuro-functional evidence for the suggested link between OFC/ACC activity, serotonin, and inhibitory control. More specifically, they suggest that OFC and adjacent regions exert an inhibitory effect on impulsive aggression through serotonergic mechanisms.

A genetic contribution to the relationship between serotonin function and impulsive aggression is supported by many studies referring to the serotonin transporter (5-HT) gene (e.g. [92, 93]) and the tryptophan hydroxylase gene [94, 95]. In addition, a positive association between the allelic variant of the MAOA polymorphism coding for high MAOA activity and self-reported aggression and impulsivity in men was also reported [89]. These findings may be indicative of a higher genotypic risk for impulsivity/aggression in males conferred by serotonin-related polymorphisms.

Meyer-Lindenberg et al. [96] found that carriers of MAOA-L had volume reductions relative to the volume in MAOA-H subjects in the rostral and dorsal ACC, the amygdala, the insula, and the hypothalamus. In addition, MAOA-L carriers showed increased amygdala activation and diminished reactivity of regulatory prefrontal areas compared with MAOA-H in a face-matching task. The authors postulate that their data identify differences in limbic circuitry for emotion regulation and cognitive control that could be involved in the association of MAOA with impulsive aggression. However, their study was performed on healthy volunteers, who were not characterised by increased levels of aggressive or violent behaviour, so that they were not studying the relationship of MAOA and violence per se.

Summary
The neurobiological data regarding antisocial personality disorder and psychopathy confirm the hypothesis that two major types of antisocial behaviour exist: reactive-impulsive aggression and proactive-instrumental aggression. While the former describes the majority of violent criminals, the latter is characteristic of the small group of psychopaths. Both groups are characterised by dysfunctional autonomic responses, disturbances of the serotonin system, and deficits in the interaction of limbic cortical-frontal and sub-cortical centres in the context of impulse control, empathy, and the processing of affects and emotions, particularly fear and anger [97].

With respect to antisocial individuals, there is strong evidence that structural or functional impairments (i.e., volume loss and decreased activity) of the frontal cortex, especially OFC and VMPFC, are associated with impulsive aggression and violent behaviour. This goes along with increased sub-cortical activity, for example in the amygdala.

In psychopaths which are characterised by proactive-instrumental aggression and psychopathy, there are deficits in the processing of negative emotional information and generally emotional hypo-responsivity exists. The majority of studies report a reduced activation of limbic centres in psychopaths compared to controls using aversive conditioning. Kiehl’s paralimbic dysfunction model describes distributed abnormalities in the amygdala, the OFC, the temporal pole, the anterior and posterior cingulate cortex, the insula, and the parahippocampal regions [69, 98]. Others found enhanced activations in the amygdala, OFC, and DLPFC during emotional learning. Most remarkably, in most studies psychopathic individuals exhibit no impairment in intellectual-cognitive abilities and theory of mind, they simply appear to have no concern for the pain and emotions of others. Successful psychopaths demonstrated even greater autonomic reactivity and stronger executive function than both the unsuccessful psychopaths and the controls. They appear to be specifically competent at internalising anger and
response inhibition, and show no impairment in intelligence, insight, or understanding of norms, which makes them particularly dangerous. Their specific neurobiological deficits remain to be elucidated.

Concluding remarks

Individuals suffering from BPD and those exhibiting antisocial personality disorders of a psychopathic or non-psychopathic nature reveal characteristic dysfunctions in the interaction of cortical and sub-cortical centers and deficits in the serotonergic system. BPD patients and non-psychopathic individuals with reactive-impulsive aggression exhibit many commonalities, such as heightened responses to emotional, especially unpleasant stimuli, a decreased level of serotonin and characteristic polymorphisms in the 5-HT transporter gene and the MAOA enzyme, but also smaller volumes of frontal brain areas and the hippocampus, decreased frontal metabolism including OFC and ACC, but increased amygdala activity, which may explain the deficits in impulse control characteristics of both groups. In psychopaths, we mostly find decreased autonomic responses and deficits in emotionality including emotional learning and empathy, while intellectual and cognitive functions seem unimpaired. Despite these findings, there are many inconsistencies, especially with respect to the activity of cortical and limbic areas. These inconsistencies could be, among others, the result of (1.) the heterogeneity of disorders, (2.) co-morbidities, (3.) inconsistent diagnoses, (4.) small sample sizes, (5.) methodological and technical insufficiencies, (6.) lack of understanding of the dynamics of the interaction between cognitive and limbic areas, as well as the interaction between cortical and sub-cortical limbic areas, and (7.) type of treatment/phase of the disease. Thus, we are far from under standing the neurobiological basis of personality disorders.

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