Unmasking feigned sanity: A neurobiological model of emotion processing in primary psychopathy

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Introduction. The neurobiological basis of primary psychopathy, an emotional disorder characterised by a lack of fear and empathy, on the one hand, and extremely violent, antisocial tendencies, on the other, is relatively unknown. Nevertheless, theoretical models that emphasise the role of fearlessness, imbalanced motivation, defective somatic markers, and dysfunctional violence inhibition mechanisms have complementary proposals regarding motivations and brain mechanisms involved.

Methods. Presently, incorporating the heuristic value of these models and further theorising on the basis of recent data from neuropsychology, neuroendocrinology, neuroimaging, and repetitive transcranial magnetic stimulation (rTMS), an attempt is made to construct a neurobiological framework of emotion processing in primary psychopathy with clinical applicability.

Results. According to this framework, defective emotional processing in primary psychopathy results from bottom-up hormone-mediated imbalances at: (1) the subcortical level; (2) in subcortico-cortical "cross-talk"; that end up in an instrumental stance at the cortical level (3). An endocrine dual-system approach for the fine-tuned restoration of these hormone-mediated imbalances is proposed as a possible clinical application.

Discussion. This application may be capable of laying a neurobiological foundation for more successful sociotherapeutic interventions in primary psychopathy.

In his now classic work The Mask of Sanity (1941), Cleckley defines psychopathy in such an elaborate and elegant manner that most of his observations have survived until today. When reading The Mask one becomes absorbed by the vivid descriptions of the emotional poverty, shamelessness, manipulativeness, superficial charm, fearlessness, and remorselessness displayed by the world's...
most cruel intraspecies predator. The psychopath is suggested to be a morally insane and untreated misfit whose violent, antisocial behaviour needs little or no stimulation; it is instrumentally driven. The motivational basis for unrestrained social aggression is provided by lack of fear and empathy, and access to prey is secured by an impenetrable mask of sanity. Cleckley’s (1941) extensive clinical descriptions of the personality characteristics of the psychopath have been widely accepted, and his definition was included in the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II). Gradually, from the DSM-III onwards, however, more behaviourally based descriptions were used, because these are more reliable measurable (Salekin, 2002). These behavioural classifications then again proved to be too narrow to distinguish psychopathy from antisocial personality disorder (ASPD). This is rather problematic because ASPD is a nonspecific classification that virtually overlaps with criminality. Up to 75% of convicted criminals in the United States can be diagnosed with ASPD on the basis of key DSM characteristics, such as the tendency to disregard the rights of others and the rules of society. These ASPD characteristics of course also apply to the psychopath; according to the DSM-IV descriptions of ASPD most psychopaths factually suffer from ASPD. The opposite can of course not said to be true, since ASPD is found in 4% of the general population whereas the prevalence of psychopathy in less than 1% (Pitchford, 2001).

A diagnostic gap was bridged with the development of the Psychopathy Checklist (PCL; Hare, 1980) and especially its revised version (PCL-R; Hare, 1991). The PCL-R is a large step forward in the definition, classification, and diagnostisation of psychopathy. The list consists of 20 items from which two main factors can be derived: Factor 1 refers to defective socioaffective characteristics and involves items, such as superficial charm, pathological lying, lack of empathy, and shallow affect, whereas Factor 2 assesses the chronic antisocial lifestyle of the psychopath with items, such as parasitic lifestyle, proneness to boredom, and impulsivity. The two factors are of course not fully independent because a chronic antisocial lifestyle logically supervenes on a defective emotional system. However, the PCL-R’s real weakness relates to the interaction between psychopathic severity and expected treatment outcome, which roots in its relationship with anxiety.

**PCL-R AND ANXIETY**

Although the PCL-R has proven to be a great improvement in the diagnostisation of psychopathy, it is a pity that it does not clearly incorporate factors of fear and anxiety (Newman & Lorenz, 2003). As a result, anxious individuals can be diagnosed with psychopathy, which is “a contradiction in terms” for the influential low fear models of psychopathy (Lykken, 1995; Patrick, 1994). To deal with this problem, researchers in the field of psychopathy have adopted the
strategy to add an anxiety scale to the PCL-R to distinguish the secondary (high anxious) from the primary (low anxious) psychopath (e.g., Newman, Patterson, Howland, & Nichols, 1990). Several studies demonstrated that the anxiety index of passive avoidance is dysfunctional in the primary psychopath exclusively (see Arnett, 1997). This begs the question whether the secondary psychopath does not better fit in a subcategory of ASPD. Moreover, the above diagnostic problems extend to questions regarding the neurobiology underlying psychopathy, because the presence or absence of fear and anxiety clearly involves different physiological substrates on both the endocrinological and the neuroanatomical level (Rosen & Schulkin, 1998).

In sum, the PCL-R was initially intended to diagnose Cleckley's psychopath, but it falls short. Since socioemotional learning is largely driven by punishments, the relative neglect of fear paradigms, such as punishment sensitivity in the assessment of psychopathy, obscures insights in therapeutic treatment outcome. Furthermore, the PCL-R's underassessment of fear and anxiety necessarily results in overdiagnosticisation. When lack of fear hallmarks psychopathy, individuals diagnosed with psychopathy should lack fear. When not, the overlap with ASPD becomes substantial and psychopathy and ASPD become fuzzy categories.

In the present review we will address hypothetical considerations about defective brain circuits and dysfunctional emotional processing in primary psychopathy.

**Psychopathy and emotional processing**

Various models on emotional dysfunction in psychopathy have been proposed since Phillippe Pinel, almost two centuries ago, coined the term *Insanity without a delirium*. The term refers to emotional dysfunction in absence of emotional distress, which typifies psychopathy. For centuries, labelling emotional behaviour as disordered has been based on the rather vulnerable observation-description method. Dysfunctions in emotional processing can, however, additionally be assessed by, for instance, the selective attentional or physiological response to threat. Hypervigilant cognitive and psychophysiological affective responses are often observed in both highly and clinically anxious subjects (Williams, Mathews, & MacLeod, 1996), while hypovigilance marks ASDP and in particular the primary psychopath (Arnett, 1997). Both the former preoccupation with environmental threat and the latter neglect of threat arguably plays an important role in the aetiology and maintenance of emotional disorders such as melancholic depression, social phobia, and psychopathy (Schulkin, 2003a; Van Honk & de Haan, 2001; Williams et al., 1996). Thus the psychopath displays an inattentiveness to threat, a risky behavioural strategy that leaves more room for attending to the rewarding aspects of the environment. In social phobia and melancholic depression, sensitivity for the punishing consequences
of (threatening) social encounters should result in socially avoidant behaviour, while in the psychopath punishment insensitivity defensibly leads to unrestrained and socially aggressive forms of behavioural approach (Arnett, 1997; Raine, 1996). In sum, hypophobia in psychopathy seems to predispose for violence and social aggression through defective inhibition in antisocial behaviour. This theoretical notion has its roots in the groundbreaking findings of Lykken (1957) that have recently been further elaborated by Patrick (1994). In the next section of this review the four most influential theoretical models of psychopathy are discussed.

THEORETICAL MODELS OF PSYCHOPATHY

Low fear model of psychopathy
The low fear model of psychopathy states that the psychopathic disturbance is rooted in and nourished by the absence of fear. Fearlessness secures for an inability to respond to and learn from the punishing consequences of antisocial and violent behaviour. Almost half a century ago David Lykken (1957) started to explore this low fear model using the concept of passive avoidance. In aversive-conditioning paradigms it was repeatedly demonstrated that psychopaths have a lesser tendency to avoid behaviour that had previously been associated with punishment in the form of mild electric shocks. Many theorists regarded fearlessness as one of the main characteristics of psychopathy (Cleckley, 1982; Fowles, 1980; Lykken, 1957). The findings of Lykken are exemplary according to Fowles (2000), because the observation of poor aversive conditioning in psychopaths later on proved to be one of the most reliable phenomena in psychopathology-related psychophysiological research. Lykken’s (1957) findings have also been supported with the use of the startle reflex as an index for fearfulness. Reduced startle reflexes to threatening visual stimuli (Patrick, Bradley, & Lang, 1993) and to imagined fearful situations (Patrick, Cuthbert, & Lang, 1994) have been demonstrated in psychopaths.

All this has led to the notion that psychopaths have problems with passive avoidance or punishment-induced behavioural inhibition. Societal control over individuals’ violent and antisocial behaviour is liable to fail in absence of punishment sensitivity, because attempts for social correction have no effect. However, explanations for poor passive avoidance in the psychopath often refer to punishment insensitivity or low levels of fear, which is somewhat weak since the notion that the preservation of behaviour that has been punished is due to insensitivity for punishment may have descriptive value but surely no explanatory value. One could perhaps better state that psychopaths do poorly on anxiety-mediated avoidance learning, and seek for an explanation on the brain-system level, where the anxiety-related physiological responses are generated and interpreted. In particular the quest for identifying neurobiological
mechanisms underlying defective passive avoidance in psychopathy would be of interest (Arnett, 1997).

Thus, the low fear hypothesis for psychopathy has found strong support during decades of research, which makes it all the more problematic that the clinical selection criterion applied, the PCL-R, does not directly assess anxiety (Newman & Lorenz, 2003). When the absence of anxiety is a pivotal feature in primary psychopathy, additional measures to index anxiety seem necessary. Moreover, the low anxious or true psychopath (Fowles, 2000) is of prime interest for scientific enquiry because the expectancy for successful psycho- or sociotherapeutic interventions in these subjects is extremely low (Salekin, 2002). Another crucial issue which relates to the psychopaths’ punishment insensitivity tends to escape attention; punishment is particularly ineffective in psychopaths when it conflicts with reward. Short-term reward is favoured even with the knowledge that this will be followed by extreme future punishment. Moreover, the motivational systems of behavioural inhibition (BIS) and behavioural activation (BAS) are mutually inhibitory (Fowles, 1980), hence the insensitivity for punishment logically allows a fuller expression of BAS, as can be seen in a hypersensitivity for reward in the psychopath. Important studies that relate to this issue have been performed by Arnett, Howland, Smith, & Newman (1993) and Arnett (1997) who showed that heart rate increases to monetary incentives (i.e., approach cues) were observed in psychopaths, but only in those who were low anxious (i.e., behaviourally inhibited). These findings fit best with Fowles’ (1980) explanation of psychopathy in terms of the balancing properties of BIS and BAS. In sum, evidence from behavioural and psychophysiological studies suggest a weak inhibition and a strong activation system in psychopathy; the motivational imbalance model of psychopathy (Arnett, 1997).

Motivational imbalance model of psychopathy

In his comprehensive review of automatic responsivity in psychopathy, Arnett (1997) heavily builds on the personality model of Gray (1987) and Fowles (1980) for the construction of an elegant framework of imbalanced motivation in psychopathy. Arnett convincingly argues for the mutually inhibitory properties of the key motivational systems and suggests that a weak BIS when connected with a strong BAS has high explanatory value in the etiology and maintenance of psychopathy. It should however be noted that this reciprocal inhibition between the BIS and BAS systems was already an important feature in Fowles’ (1980) model. Arnett (1997), however, evaluates a large amount of data and specifically defends the notion of motivational imbalance in the “primary” form of psychopathy. It is in this conception of motivational imbalance that defective inhibition resulting from weak BIS allows fuller expression of the BAS, behaviourally expressed in disinhibition accompanied by reward-seeking tendencies (Arnett, 1997; Lovelace & Gannon, 1999). In secondary psycho-
pathy, the strength of BIS (anxiety) should be less weakened and perhaps of a more fluctuating nature, opening the possibility for successful sociotherapeutic intervention (cf. Salekin, 2002). Simply stated, when categorised in the above fashion, the secondary psychopath is unpredictably bad, but the primary psychopath is bad to the bone.

However, although there is considerable evidence of weak BIS in psychopathy, the evidence for strong BAS is far less convincing. This is most likely due to the fact that research in the latter area is much scarcer (Arnett, 1997). Some evidence is nevertheless available in the larger heart rate responses or increases to reward in count-up paradigms (e.g., Arnett, Smith, & Newman, 1997; Hare, Frazelle, & Cox, 1978) a true manifestation of enhanced sensitivity for the rewarding aspects of the environment in psychopathy. Nevertheless, evidence suggests a kind of imbalance in the psychopaths’ BIS and BAS. The mutually inhibitory nature of these systems is responsible for the fact that the insensitivity for punishment observed in psychopathy is in particular evident when reward is pending (Arnett, 1997).

In the Arnett (1997) review, this concept of mutual inhibition between the BIS and the BAS is elaborated on, and the imbalanced strength of systems found in psychopathy is argued to find its reflection in depression, where strong BIS in conjunction with an already weakened BAS results in pathological withdrawal (Van Honk, Hermans, Putnam, Montagne, & Schutter, 2002b). This should particularly be true in a psychopathological state frequently observed; anxious depression (Rosen & Schulkin, 1998). In agreement, recent studies that investigated the connectional nature of the mutually exclusive BIS-BAS on basis of questionnaires have found evidence for strong BIS and weak BAS in depression, and crucially in the present respect strong BAS and weak BIS were observed in psychopathy (Kasch, Rottenberg, Arnow, & Gotlib, 2002; Lovelace & Gannon, 1999). It seems that a continuum of prototypical psychopathology can be constructed on the basis of the relative imbalanced involvement of approach- and withdrawal-related emotion. Anxious depressed subjects can be characterised by extreme forms of social withdrawal, whereas the psychopath shows uninhibited approach tending towards a violent, antisocial level.

Arnett’s mutually inhibitory system can easily be fitted within an influential theoretical framework of the neurobiology of emotion that largely builds on data from patients with lesions to the orbitofrontal and medial regions of the prefrontal cortex (OMPFC); the somatic marker hypothesis (SMH).

**Somatic marker hypothesis of psychopathy**

According to Damasio’s (1994) SMH, emotional learning is established by somatic or bodily feelings that consciously or unconsciously mark behaviours that have negative or positive outcome for the individual (Tranel, Bechara, & Damasio, 2000; but see Maia & McClelland (2004) for a critical note). Hence,
adaptive emotional learning depends on the balanced induction of punishment-related inhibition and reward-related enhancement of specific behavioural choices. Decision making is thus dependent on bioregulatory markers that signal incentives for approach or avoidance in an attempt to maintain homeostasis and ensure survival. Emotions occupy the top level of this bioregulatory response system and neurological evidence indicates that damage to the OMPFC or the amygdala precludes the ability to guide decisions advantageously because somatic (emotional) signals can not be read or are simply absent (Bechara, Damasio, Damasio, & Lee, 1999).

With respect to psychopathy, the SMH seems to provide a neurobiological foundation for Arnett’s (1997) model of motivational imbalance, by framing the neural substrates of adaptive and balanced motivational tendencies that guide emotional decision making (Damasio, 1994). In the proposed neural circuitry of these motivated choices, the key roles are again played by the amygdala and the OMPFC (Bechara et al., 1999). Evidence largely stems from experiments with the Iowa gambling task. In this task subjects are instructed to try to earn as much money as possible while drawing cards from four different decks (Bechara, Damasio, Damasio, & Lee, 1994). In the task, decisions to choose from decks of cards should become motivated by preprogrammed punishment and reward schedules. Insensitivity for punishment together with a strong reward dependency results in impaired performance. The fact that impaired gambling performance has been demonstrated in both clinical (Blair, Colledge, & Mitchell, 2001a; Mitchell, Colledge, Leonard, & Blair, 2002) and subclinical psychopaths (Van Honk, Hermans, Putman, Montagne, & Schutter, 2002b) links the SMH to psychopathy. Although the SMH initially emphasises the role of the OMPFC in emotional learning, the amygdala is also crucial. Patients with damage to either the OMPFC or the amygdala show defective decision making on the Iowa gambling task (Bechara et al., 1999). While amygdala patients are unable to grasp the situation’s affective value because markers are simply absent, OMPFC cannot interpret affective value for guiding their decisions advantageously. Important in this respect, preliminary data from neuroimaging studies point at defective OMPFC-amygdaloid networks in psychopathy (Veit et al., 2002).

Another important theorist in the field of psychopathy is James Blair, and his theoretical framework in particular distinguishes primary from secondary psychopathy.

Defective violence inhibition mechanisms in primary psychopathy

According to Blair (2003b) the SMH builds on evidence coming from patients with so-called “acquired sociopathy” whose aggression is impulsive and reactive in nature (i.e., frustration/threat-induced) rather than instrumental and goal-directed. According to Blair, both instrumental and reactive forms of
aggression can be observed in primary psychopaths, but secondary psychopaths demonstrate almost exclusively reactive aggression. In this model, the orbitofrontal cortex is more strongly involved in reactive aggression, while the amygdala is particularly involved in instrumental aggression.

Blair (2003b) furthermore proposes a violence inhibition mechanism (VIM) that relates in particular to the primary psychopath. The VIM theory argues that a particular neurocognitive deficit plays a major role in the etiology of psychopathy. Putting relatively more weight on lack of empathy and building on ethological work in social animals by Lorenz (1966) and Eibl-Eibesfeldt (1970), evolved signalling mechanisms for the control of social aggression are suggested. The rule is that when a conspecific aggressor encounters submissive cues, such as the display of fear, attack will be terminated by the VIM. The VIM secures obedience to the rule in a fully automatic fashion. Activation of VIM by cues of fear and distress starts up the “empathic” response that goes accompanied by decreases in autonomic activity and attention to the victim. Although Blair is not very explicit on this, it is with respect to primary psychopathy very important to distinguish between cognitive and affective forms of empathy. The primary psychopath should of course possess “mind reading skills” to predict the behaviour of a victim to be, but lacks the affective forms of empathy that work by feeling and understanding other people’s pleasures and pains (Decety & Jackson, 2004). It should furthermore be noted that Blair sees primary psychopathy as a developmental disorder carrying a breakdown in social moralisation. The neurological locus of this “neurocognitive” impairment in psychopathy is the amygdala, and when seen in the light of the ability to recognise the submissive cue of fear this view also finds support. One of the most replicated findings in neuropsychological research is the relationship between the amygdala and the processing of fearful faces (Calder, Lawrence, & Young, 2002). Moreover, it has been demonstrated repeatedly that subjects with psychopathic characteristics are impaired in the recognition of fearful facial expressions (Blair, 2003a, 2003b; Montagne et al., 2005). Moreover, Blair’s theory not only pays attention to lack of empathy but also to lack of fear (Blair, 2003b), and there is evidence for poor passive avoidance (e.g., Lykken, 1957) and an attenuated fear-potentiated startle in psychopathy (Herpertz et al., 2001). In conclusion, according to Blair, amygdala dysfunction is revealed in primary psychopathy in the face of danger or when affective empathy is requested. Although the model of Blair is rather different from the other models discussed above there are commonalities.

Theoretical integration

It is most interesting to observe that the above theoretical proposals are not contradictory in any strong manner, surely not when evaluated in terms of fundamental issues of the sensitivity to punishment and reward. The low fear
model of Lykken findings (1957) was especially focused on the aspects of fear and punishment sensitivity. In recent years, however, theorists have directed more attention to the involvement of rewarding properties of the environment as explicitors of punishment insensitivity in psychopathy (for a review, see Arnett, 1997). Thus, the low fear model preceded and partly founded the motivational imbalance model of psychopathy (Arnett, 1997; Fowles, 1980). Next, Damasio’s SMH discusses a neurobiological principle of balanced and imbalanced motivational stances by proposing involvement of a neural network encompassing the OMPFC and the amygdala. Punishment- and reward-learning seems to depend on OMPFC's accessibility to amygdala-generated bodily signals. Finally, Blair (2003a, 2003b) discusses a specific subcortically driven neurobiological mechanism (VIM) seemingly defective in psychopathy. Nevertheless, in its manifestations this defect can be seen as a specific imbalance in the sensitivity for punishment and reward. Extreme reward sensitivity predisposes for social aggression, but the final execution of aggression needs disinhibition which is provided by low fear and empathy (cf. Keltner, Moffitt, & Stouthamer-Loeber, 1996). In the remainder of this review we will attempt to integrate the above models of dysfunctional emotional processing in primary psychopathy into a neurobiological triple balance model of emotion that serves as a research heuristic with possible clinical applications. According to this model, three neurobiological balances in processing punishments and rewards and control homeostasis in socioemotional functioning: a subcortical balance (1); a subcortico-cortical communication balance (2); and a cortical balance (3). It is furthermore proposed that the end-products of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes, testosterone and cortisol play crucial roles in setting these emotional balances. The details of how this translates to the processing of punishment and reward, and primary psychopathy are discussed below.

TRIPLE BALANCE HYPOTHESIS OF EMOTION

1. Subcortical balance

A fine-tuned balance in reaction to punishment and reward is crucial for survival and signifies psychobiological homeostasis (Ressler, 2004). Extremities in the processing of punishment and rewards lead to emotional disorders (Van Honk et al., 2004). From an evolutionary point of view, approach- or withdrawal-related response to reward or punishment are illustrated by the fight-flight cascade that is initiated in subcortical affective circuits and controlled by endocrine-autonomic nervous system interactions (Decatanzaro, 1999). A crucial hypothesis in the triple balance model of emotion is that the end-products of the HPA and (HPG) axes, the steroid hormones cortisol and testosterone are pivotally involved in homeostatic emotion regulation through their antagonistic actions on the biological and psychological level. This
antagonism begins with the mutually inhibitory functional interaction between the HPA and HPG axis (Viau, 2002), which concurs with mutually inhibitory connection between the BIS and the BAS (Arnett, 1997). Cortisol suppresses the activity of the HPG axis at all its levels, diminishes the production of testosterone and inhibits the action of testosterone at the target tissues (Johnson, Kamilaris, Chrousos, & Gold, 1992). Testosterone in its turn inhibits the stress-induced activation of the HPA axis at the level of the hypothalamus (Viau, 2002). The steroids cortisol and testosterone are suggested to act on the brain by binding to amygdaloid-centred steroid-responsive neuronal networks (Wood, 1996) where they regulate and facilitate the neuropeptide gene expression that changes the probability of approach (testosterone) or withdrawal (cortisol) when confronted with environmental threat (Schulkin, 2003). Thus, the steroids cortisol and testosterone are capable of inducing neurochemical changes advancing from the subcortical level that influence the way in which organisms act in the presence of threat.

Cortisol

The glucocorticoid cortisol is a crucial neuroendocrine mediator of the emotion fear. Elevated levels of cortisol act on the amygdala to facilitate corticotropin-releasing hormone (CRH) gene expression that potentiates the state of fear (Rosen & Schulkin, 1998). In agreement, evidence indicates a role for cortisol in the disorders of fear and anxiety and in the anxious manifestations of depression. High levels of cortisol have been observed in anxious depressed patients (Schulkin, 2003) and also in nonclinical anxious (Brown et al., 1996) and depressed subjects (Van Honk et al., 2003a). In contrast, and in support of the low fear model of psychopathy (Lykken, 1957), low levels of cortisol have been observed in subjects with aggressive antisocial tendencies (McBurnett et al., 1991; Vanyukov et al., 1993; Virkkunen, 1985). Inconsistent findings have however also been reported (Schulz, Halperin, Newcorn, Sharma, & Gabriel, 1997), but can be explained in terms of secondary forms of psychopathy (McBurnett, Lahey, Rathouz, & Loeber, 2000) and put emphasis on differential emotion processing in primary and secondary psychopathy (Arnett, 1997). In sum, the association between low levels of cortisol and low fear vs. high social aggression suggests a possible role for cortisol in the primary form of psychopathy. Such a role would nicely fit Arnett’s motivational imbalance model (Arnett, 1997) that emphasises the role of punishment insensitivity (fearlessness) and reward dependency (anger proneness) in primary psychopathy. Moreover, as noted earlier, the insensitivity for punishment together with a strong reward dependency results in impaired performance on the Iowa gambling task. Indeed, such impaired decision-making performance was recently observed in subjects with low levels of cortisol (Van Honk, Schutter, Hermans, & Putman, 2003b).
Testosterone

Opposed to the amplifying effects of cortisol on fear, testosterone has not only rewarding properties, but also leads to reductions in fear (Boissy & Bouissou, 1994). Elevated levels of testosterone should in theory lead to a more disadvantageous pattern of decision making on the Iowa gambling task. This hypothesis was recently confirmed when the effects of a single administration of testosterone on decision making in the gambling task were investigated. Testosterone was hypothesised to induce a shift in motivational balance towards decreased punishment sensitivity and enhanced reward sensitivity. As expected, after testosterone administration subjects made overall more disadvantageous decisions on the task (Van Honk et al., 2004). Animal research has already shown that testosterone treatment reduces the sensitivity for punishment (Boissy & Bouissou, 1994) while enhancing the sensitivity for reward (Carr, Fibirger, & Phillips, 1989). These changes would precisely induce the imbalance in the core motivational tendencies that predisposes for primary psychopathy (Arnett, 1997; Fowles, 1980). In concordance, elevated testosterone levels have been related to psychopathy as measured on the Karolinska Scales of Personality (KSP; Stalnheim, Eriksson, Von Knorrig, & Wide, 1998). Furthermore, testosterone has been associated with antisocial tendencies, such as aggressive dominance and criminal violence, in both males (Dabbs, Carr, Frady, & Riad, 1995; Dabbs & Morris, 1990) and females (Dabbs & Haregrove, 1997; Dabbs, Ruback, Frady, Hopper, & Sgoutas, 1988). Importantly in this respect, testosterone is argued to be involved in instrumental forms of aggression (Van Honk et al., 2004), which are rather selectively observed in the primary psychopath (Blair, 2001, 2003a). Note, however, that a role of testosterone in primary but not secondary psychopathy is far from evident. Interestingly, low serotonergic central neurotransmission strongly relates to the reactive forms of aggression observed in secondary psychopathy, and reactive aggression manifests itself often in highly comorbid forms involving anxiety and depression (e.g., borderline disorder). Given the evidence for fear-reducing and antidepressant properties of testosterone (Van Honk, Peper, & Schutter, 2005), it might be argued that in primary psychopathy heightened levels of testosterone go accompanied by relatively normal serotonin activity while in secondary psychopathy low serotonin and high testosterone levels in the central nervous system predispose for more impulsive forms of aggression (cf. Birger et al., 2003). Given the evidence for testosterone and serotonin inhibiting each other’s actions (McEwen & Seeman, 2003) the neurobiological interactions seem to fit best in secondary psychopathy.

In the neurobiological mechanisms underlying the effects of cortisol and testosterone on the sensitivity for punishment and reward construct, a crucial role seems reserved for the amygdala. As noted, steroid hormones act by binding to amygdala-centred steroid-responsive neuronal networks in the brain (Meisel
Moreover, animal data indicate that cortisol acts on the amygdala to facilitate CRH gene expression which increases the sensitivity for punishment (Schulkin, 2003a) whereas testosterone facilitates vasopressin gene expression at the amygdala which increases the sensitivity for reward (DeVries, DeVries, Taymans, & Carter, 1995).

2. Subcortico-cortical balance

Appropriate communication between the subcortical and cortical regions of the emotional brain is argued to be crucial for healthy socioemotional functioning (Mayberg et al., 1999). Concerning amygdala-OMPFC communication, for instance, the amygdala attributes affective value to a stimulus, while the OMPFC provides for the more complex affective evaluation that plays a role in the decision for proper action. In agreement, patients with amygdala lesions have problems in assigning affective value to a stimulus and OMPFC patients have difficulties in making appropriate reactions to emotional situations (Bechara et al., 1999). Thus these brain structures highly depend on each other, with the workings of the amygdala finding their appreciation on the OMPFC level, and the OMPFC depending on correct amygdala input to guide emotional behaviour appropriately. Not unexpectedly, neuroimaging data from psychopaths (Kiehl et al., 2001; Veit et al., 2002) and from ASPD patients (Raine, Lencz, Bihrlle, Lacasse, & Colletti, 2000) can easily be interpreted in terms of communication deficits between the amygdala and OMPFC.

In the latter study, Raine et al. (2000) found reductions in PFC grey matter in ASPD diagnosed inmates, accompanied by reductions in skin conductance, which is an index for fear (Fowles, 2000). It must be noted that both primary and secondary psychopaths were likely present in the ASPD population of Raine et al. (2000). Nevertheless, theoretical considerations of Damasio (2000) pinpointed the abnormalities observed by Raine to the orbitofrontal cortex (OFC). To provide more definitive answers concerning a role of the OFC in skin conductance, Van Honk et al. (2001a) transiently reduced OFC grey matter excitability of eight normal subjects by applying inhibitory repetitive transcranial magnetic stimulation (rTMS). Significant reductions in skin conductance were shown, consistent with the findings of Raine et al. (2000) and the theoretical considerations of Damasio (2000). These rTMS data might have implications for treatment protocols in psychopathy since it indicates that rTMS is able to modulate punishment sensitivity at the psychophysiological level by changing neuronal excitability of the OFC. Note that fast rTMS over the fronto-polar cortex should enhance OFC activity and upgrade the inhibitory functions of the OFC (Sack & Linden, 2003) and may thus upgrade weakened punishment learning.

Recent findings suggest that subcortico-cortical communication is particularly sensitive to steroid hormone manipulation. This evidence builds on an evolutionary theory wherein the phylogenetically different brain systems relate
to the subcortically generated slow wave and cortically generated fast wave oscillations as indexed with electroencephalography (EEG) (Knyazav & Slobodskaya, 2003; Schutter & Van Honk, 2004). Relative increases or decreases in subcortico-cortical “cross-talk” are computed by correlating the change in power between the low and high frequency bands, and it has been repeatedly demonstrated that increased subcortico-cortical cross-talk as indexed by EEG is accompanied by elevated punishment sensitivity (Knyazev & Slobodskaya, 2003; Knyazev, Savostyanov & Levin, 2004). On the endocrine level, increased levels of cortisol have been associated with enhanced punishment relative to reward sensitivity and are accompanied by increased subcortico-cortical cross-talk (Schutter & Van Honk, 2005). This might not only explain the relationships between cortisol and prefrontal asymmetry discussed, but also the absence of a relation between both testosterone and left-sided frontal asymmetry since in an opposite fashion, reductions in subcortico-cortical communication have been observed after administration of testosterone (Schutter & Van Honk, 2004). The cortical cognitive-emotional system in the end depends fully on the primordial subcortical emotional systems to get fuelled with emotion (Panksepp & Panksepp, 2000). Since testosterone, at least to an extent, decouples the cortical and the subcortical regions (Schutter & Van Honk, 2005), the cortical processing mode becomes more purely cognitive; thus cold and instrumental.

3. Cortical balance

Although in very simple animals, the subcortical affective circuits in the brain are fully responsible for the reflexive responses to punishment and reward (Panksepp & Panksepp, 2000) in the course of evolution the neocortex expanded and the left and the right prefrontal cortices became involved in more sophisticated forms of approach and withdrawal (Davidson, 1992). Multiple hypotheses have been postulated regarding the asymmetrical involvement of the cerebral cortex in emotional processing. The right hemisphere hypothesis, the prevalent view for more than a century (Jackson, 1887), argues that most of our emotional processing is biased to the right hemisphere (Borod, 1993). However, evidence for this notion is largely based on lesion studies with human patients and animals that not only have methodological weaknesses in terms of plasticity problems but are also hampered by the fact that lesions can go accompanied by defective inter- and intrahemispheric cross-talk (Leuchter et al., 1997).

Moreover, the right hemisphere hypothesis has recently lost even more ground. The work of Davidson and colleagues who recorded electrical brain activity and repeatedly found evidence for the lateralisation of approach and withdrawal related emotion led to the valence hypothesis. This hypothesis states that the left prefrontal cortex (PFC) is involved in approach-related positive affect and the right PFC in withdrawal-related negative affect (Davidson, 1992). Although the link between approach- and withdrawal-related affect and anterior asymmetry
proved highly reliable over the years, the positive-negative distinction became difficult to defend in recent years especially with respect to the "negative" emotion anger (Harmon-Jones, 2003). Anger is an energising emotion driven by motives of reward with tendencies for aggression (Harmon-Jones, 2004), the prototypical emotion of approach (Van Honk & Schutter, 2005).

Findings and theoretical elaborations of Harmon-Jones (2003) provide for a revision of common notions in approach- and reward-related psychopathological processing. On basis of an extensive line of evidence demonstrating links between the left PFC, anger, and aggression, Harmon-Jones (2003, 2004) proposed a model of motivational direction that drops the "positive-negative" valence dimension and simply suggests that approach-related emotion is linked to the left PFC and the withdrawal-related emotion to the right PFC.

Support for this new wave in anterior asymmetry and emotion was provided by data from rTMS. Using the proper frequency parameter settings, rTMS enables transient changes in asymmetrical brain activation (Van Honk & Schutter, 2004). For instance, a deactivation of the right prefrontal cortex induces reductions in contralateral inhibition between the hemispheres ending up in left prefrontal activation (Schutter, Van Honk, d'Alfonso, Postma, & De Haan, 2001). In accordance with the dimensional model of approach and withdrawal of Harmon-Jones (2003) the induction of relatively more left prefrontal activity results in reductions in attention to fearful facial expressions and enhanced attention to angry facial expressions (Van Honk & Schutter, 2004; Van Honk et al., 2002a; Van Honk, Schutter, d’Alfonso, Kessels, & De Haan, 2002c; d’Alfonso, Van Honk, Hermans, Postma, & De Haan, 2000). Finally, concurring with our data on cortisol and testosterone, recent evidence was found for anterior asymmetry being predictive for the balance between the sensitivity for punishment and reward as assessed by the Iowa gambling task (Schutter, De Haan, & Van Honk, 2004). This instigates the idea that balanced homeostasis between emotional approach and withdrawal (Arnett, 1997; Van Honk & Schutter, 2005) can work by way of the antagonistic features of the emotions fear and anger (Keltner et al., 1995). Note that the core negative emotions are, in such a view, no longer stigmatized but their pivotal role in cognitive and motivational aspects of attention, learning, and decision making is recognised, as well as their indispensable counter-regulatory socioemotional functions and crucial life-saving properties (Dimberg & Öhman, 1996; Van Honk et al., 2001b). Moreover, on the notion that evolution provided organisms with a rich set of mechanisms to maintain homeostasis (Schulkin, 2003b), the idea that left-dominant asymmetrical processing in the PFC would be associated with psychobiological well-being seems counterintuitive (but see Davidson, 2004). Reasoned from the evolutionary perspective the homeostatic state (or psychobiological well-being) is more likely symmetrical in nature and defensibly an emergent property of the balance between emotional approach and withdrawal (Van Honk & Schutter, 2005).
Several reports link fearfulness and high levels of cortisol to right-sided dominance in frontal asymmetry (Buss et al., 2003; Kalin, Larson, Shelton, & Davidson, 1998; Tops et al., 2004) but there is no evidence for such inter-relationships between testosterone, aggression, and left-sided dominant frontal asymmetry. This could be explained by the fact that testosterone induces hypocoupling whereas cortisol induces hypercoupling between the subcortical and cortical structures (Schutter & Van Honk, 2004, 2005). The cortisol-mediated anxious-depressive stance is clearly reflected on the cortical level as a result of subcortico-cortical hypercommunication, but the psychopathic stance remains “masked in sanity” because testosterone decouples the upper and the lower brain structures.

**Triple balance model of emotion applied to primary psychopathy**

In the preceding section, the triple balance model of emotion was introduced. It was stated that hormonal imbalances induce motivational imbalances on and between the different levels of the brain. In the primary psychopath, this hormonal imbalance should be observed ratio-wise as lowered activity of the HPA vs. heightened activity of the HPG axis. This ends up in relative low levels of cortisol vs. high levels of testosterone, the hormonal imbalance that provides for a motivational stance of low punishment vs. high reward sensitivity, on (1) the subcortical level (DeVries et al., 1995; Schulkin, 2003a; Van Honk et al., 2004). This imbalance also reduces (2) subcortico-cortical communication (Schutter & Van Honk, 2004, 2005), depriving the cortical balance (3) from necessary emotion input for guiding social behaviour appropriately (Blair, 2003b). This triple balance model of emotion might have potential for the diagnosis and treatment of primary psychopathy. The standard method of diagnosis by observation and interview could be supplemented with and compared to a fine-grained neurobiological measurement of the activity of the HPA and HPG axes (Balance 1). Furthermore, EEG recordings might be applied to provide information on the subcortico-cortical cross-talk (Balance 2), and frontal asymmetry of emotion (Balance 3). If imbalances (Figure 1) are observed they could be restored in a bottom-up manner by endocrinological manipulations targeting the activity of the HPA and HPG axis or the levels of their end-products (Viau, 2002). Research in clinical populations is however necessary to find under what tonic levels of activation of the endocrine axes the ratio imbalances reveal themselves in particular. Nevertheless, although we must take a provisional stance on the issue, an endocrinological dual systems approach that aims to restore the imbalances within and between the HPA and HPG axes may have the potential for laying a neurobiological foundation for more successful psycho- and sociotherapeutic interventions in primary psychopathy.
Figure 1 delineates the main features of the triple balance model of emotion and shows how it relates to primary psychopathy.

**DISCUSSION**

In this review, concurring theoretical proposals have been outlined regarding the relative involvement of the core motives punishment and reward sensitivity in primary psychopathy. Fitting with these notions, experimental evidence from several lines of neurobiological research suggest specific neuroanatomical and neurohormonal substrates to be defective in psychopathy. The primary psychopath shows an extreme motivational imbalance in terms of low sensitivity for punishment and high sensitivity for reward, which is argued to depend importantly on imbalances in the activity in and between the HPA and HPG axes, measured in terms of the ratio of cortisol and testosterone levels. An imbalanced ratio will be reflected in: (1) a reward-driven motivational imbalance at the subcortical level; (2) defective subcortico-cortical communication; and (3) an emotionally flattened cortical stance. An endocrine dual-systems approach was proposed for restoring the motivational imbalances observed in psychopathy working by way of fine-tuned cortisol and testosterone manipulations to sensitise...
the psychopath’s emotional system for traditional therapeutic approaches. This method might have efficacy in the treatment of primary psychopathy, a still untreatable emotional disorder that distinguishes itself particularly by bringing greater misery to victims and society than to the patients themselves.

REFERENCES


