Socially Explosive Minds: The Triple Imbalance Hypothesis of Reactive Aggression

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ABSTRACT The psychobiological basis of reactive aggression, a condition characterized by uncontrolled outbursts of socially violent behavior, is unclear. Nonetheless, several theoretical models have been proposed that may have complementary views about the psychobiological mechanisms involved. In this review, we attempt to unite these models and theorize further on the basis of recent data from psychological and neuroscientific research to propose a comprehensive neuro-evolutionary framework: The Triple Imbalance Hypothesis (TIH) of reactive aggression. According to this model, reactive aggression is essentially subcortically motivated by an imbalance in the levels of the steroid hormones cortisol and testosterone (Subcortical Imbalance Hypothesis). This imbalance not only sets a primal predisposition for social aggression, but also down-regulates cortical–subcortical communication (Cortical-Subcortical Imbalance Hypothesis), hence diminishing control by cortical regions that regulate socially aggressive inclinations. However, these bottom-up hormonally mediated imbalances can drive both instrumental and reactive social aggression. The TIH suggests that reactive aggression is differentiated from proactive aggression by low brain serotonergic

Jack van Honk was supported by a High Potential Grant from Utrecht University, The Netherlands. The research of Eddie Harmon discussed in this article was supported by the National Science Foundation (BCS-0552152 and BCS-0643348). Barak Morgan was supported by a Professional Development Program grant from the Medical Research Council of South Africa. Dennis J.L.G. Schutter was supported by an Innovational Research Grant (452-07-012) from the Netherlands Organization for Scientific Research (NWO).

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Journal of Personality 78:1, February 2010

DOI: 10.1111/j.1467-6494.2009.00609.x

function and that reactive aggression is associated with left-sided frontal brain asymmetry (Cortical Imbalance Hypothesis), especially observed when the individual is socially threatened or provoked. This triple bio-behavioral imbalance mirrors an evolutionary relapse into violently aggressive motivational drives that are adaptive among many reptilian and mammalian species, but may have become socially maladaptive in modern humans.

In many reptilian and mammalian species, reactive social aggression is highly adaptive in obtaining key resources such as food, shelter, and mating partners (Mazur & Booth, 1998; van Honk et al., 2001). However, this is much less the case in modern humans, for whom much of the adaptive value of reactive social aggression is lost. Socially aggressive behaviors in humans may even be maladaptive, because they often lead to serious societal punishment. Nonetheless, recent data from psychological and neuroscientific research indicate that similar neurobiological states may still trigger reactive social aggression in human and nonhuman animals (Blair, 2004; Hermans, Ramsey, & van Honk, 2008). In this review we argue that imbalanced processing on several interacting levels of the emotional brain underlies reactive aggression. These emotive imbalances should be viewed within their current social contexts, because reactive aggression is evaluated differently in peaceful than in life-threatening (i.e., warfare) conditions. Arguing from Hughling Jackson's (1887) principle of dissolution, social brain systems show an evolutionary relapse in times of war, when more ancient aggressive behavioral predispositions become adaptive once more.

Social aggression has been defined in many ways, but for heuristic purposes, we will restrict this discussion to the two main subtypes, proactive aggression and reactive aggression. In an earlier review (van Honk & Schutter, 2006b), we aimed to construct a psychobiological framework of proactive human aggression in which psychopathy was highlighted. Presently, the focus is on reactive human aggression, and the model offered will be more dimensional in nature. Rightfully criticized when taken absolutely (Anderson & Bushman, 2002), the concepts of proactive and reactive aggression have served as excellent heuristic models in research. Proactive and reactive aggression describe objectively observable divergent behaviors. In essence, the difference is clear-cut: Proactive aggression conveys premeditated social violence, and thus planned behavior, and is typically not associated

with frustration or response to immediate threat. Reactive aggression, on the other hand, is not premeditated but characterized by the display of anger, loss of control, impulsiveness, and heightened sensitivity/responsivity to social threat (Siever, 2008).

CORE BRAIN CHEMICALS OF REACTIVE AGGRESSION

A brain chemical thought to underlie social aggression, and sex differences in social aggression, is the male-sex hormone testosterone (Archer, 2006). Testosterone increases aggressive behavior in many reptilian and mammalian species (Archer, 1988), and there is evidence that the administration of testosterone potentiates aggression in humans (Brain, 1979). In addition, aggression is reduced by castration in animals and humans (van Goozen, Cohen-Kettenis, Gooren, Frijda, & van de Poll, 1995). However, the link between testosterone and aggression appears to be much stronger in nonhuman animals (Mazur & Booth, 1998). This may, in part, be due to our well-developed prefrontal cortex (PFC): PFC regulatory mechanisms, to an extent, may enable humans to escape direct hormonal control of social behavior (Curley & Keverne, 2005). On the other hand, absent relations between testosterone and aggression mostly come from studies using self-reports, perhaps not the best method to index hormone–behavior associations (van Honk & Schutter, 2007). Indeed, there is evidence supporting the point that testosterone better predicts observer-rated human aggression. Testosterone levels have repeatedly been associated with observer-rated conduct disorder problems and violent reactive aggression in large populations of both males and females (e.g., Dabbs, Carr, Frady, & Riad, 1995; Dabbs & Hargrove, 1997; Dabbs & Morris, 1990). The studies of James Dabbs that applied observer ratings in prison populations leave little doubt about testosterone being implicated in reactive aggression in humans.

Even though testosterone plays a role in human aggression, it is unlikely that it is the only steroid hormone involved. There is now abundant evidence for a diametrically opposite link between cortisol and social aggression. Low levels of cortisol have been observed in subjects with high levels of behavioral activation, socialization problems, and violently aggressive antisocial tendencies (e.g., McBurnett et al., 1991; Vanyukov et al., 1993; Virkkunen, 1985). Critically, testosterone and cortisol are the end products of the hypothalamic–

pituitary–gonadal (HPG) and hypothalamic–pituitary–adrenal (HPA) axes. These endocrine axes have antagonistic—mutually inhibitory—properties (Viau, 2002) that may have explanatory value in understanding the psychobiology of not only fear and anxiety but also aggression (van Honk, Peper & Schutter, 2005; van Honk & Schutter, 2006a). Crucially, whereas heightened cortisol predisposes one to fear, low cortisol seems to predispose one to aggression (Schulkin, 2003). Cortisol specifically facilitates gene expression of corticotrophin releasing hormone (CRH) in the amygdala, which, in turn, increases states of fear, punishment sensitivity, and behavioral inhibition (Schulkin, 2003; cf. van Honk, Schutter, Hermans, & Putman, 2003). High cortisol levels have been observed in anxious depressed patients (Schulkin, 2003) and in nonclinical anxious and depressed subjects (Brown et al., 1996; van Honk, Kessels, et al., 2003).

Interestingly, testosterone exerts diametrically opposite effects from cortisol. In many species testosterone has behavioral activating, aggression inducing, and reward sensitizing properties, with correspondent reductions in fear and social avoidance (Boissy & Bouissou, 1994; Hermans, Putman, & van Honk, 2006). Revealing are data from the Iowa gambling task (Bechara, Damasio, Damasio, & Anderson, 1994), which indexes the balance between the sensitivity for punishment and reward. When this balance points to low punishment–high reward sensitivity (as measured by the BIS-BAS scales; Carver & White, 1994), disadvantageous decision making on the Iowa gambling task is observed (van Honk, Hermans, Putman, et al., 2002). Testosterone administration in young healthy women shifts the balance to this stronger sensitivity for reward, observed as more risky, disadvantageous decision making (van Honk et al., 2004). This finding is consistent with animal research showing that testosterone treatment reduces the sensitivity for social punishment (Boissy & Bouissou, 1994), but enhances the sensitivity for reward (Carr, Fibirger, & Phillips, 1989). Interestingly, a correlational study indicates that cortisol does the opposite on the Iowa gambling task, that is, it leads to more advantageous decision making, presumably through shifting the balance to a stronger sensitivity for punishment. Consequently, at the other end of the continuum, disadvantageous decision making on the Iowa gambling task is seen in subjects with relatively low levels of cortisol (van Honk, Schutter, et al., 2003).

Mutually antagonistic properties of the hormones cortisol and testosterone can be observed not only on the psychobiological but

also on the neurobiological level. This starts off with the mutually inhibitory functional connection between the HPA and HPG axes (Viau, 2002). 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; Tilbrook, Turner, & Clarke, 2000). Testosterone, in turn, inhibits the stress-induced activation of the HPA axis at the level of the hypothalamus (Viau, 2002). Crucially, in one of their core action mechanisms, these steroid hormones bind to amygdala-centered, steroid-responsive neuronal networks (Wood, 1996) that regulate and facilitate neuropeptide gene expression. On the behavioral level, animal data show that testosterone elevates vasopressin gene expression at the amygdala, thereby increasing the likelihood for behavioral approach (Schulkin, 2003). Cortisol, on the other hand, increases amygdaloid CRH gene expression and promotes behavioral withdrawal (Schulkin, 2007).

We argue that the steroid hormones testosterone and cortisol play a critical role in social aggression. More specifically, the testosterone–cortisol ratio hypothesis proposes that high levels of testosterone together with low levels of cortisol predispose one toward social aggression (van Honk & Schutter, 2006a). Vital support for this hypothesis comes from recent research in adolescent boys and girls. First and most important is the study of Popma et al. (2007), which found significant positive relationships between testosterone and overt aggression exclusively in adolescent male delinquents with low cortisol levels. More indirect evidence is provided by Pajer et al. (2006), who observed heightened testosterone and lowered cortisol relative to the testosterone precursor dehydroepiandrosterone sulfate in girls with conduct disorder. Finally, recent social psychological data from the group of Robert Josephs (Mehta & Josephs, 2008) provide evidence for enhanced competitive aggression in men with high testosterone–low cortisol ratios in an experimental social aggression paradigm.

Returning to the proactive–reactive aggression distinction, it should be noted that neither baseline testosterone nor cortisol, nor the ratio of these hormones at baseline, predicts the reactive form of aggression in particular. Both proactive and reactive aggressive motive drives seem to be facilitated by high testosterone–cortisol ratios (van Honk & Schutter, 2006b). The neurotransmitter serotonin may, in the context of the high testosterone–cortisol ratio, play a critical

role in differentiating proactive and reactive aggression. Elaborating on earlier notions (van Honk & Schutter, 2006b), we want to propose that lowered central serotonin transmission combined with high testosterone–cortisol ratios predispose one toward reactive aggression. There is evidence for a connection between low central serotonin transmission and social aggression (e.g., Miczek et al., 2007), but a plethora of psychopathologies, including social anxiety, depression, and OCD, also point to abnormalities in serotonergic function. Nonetheless, low brain serotonin turnover is thought to underlie relations between impulsive behavior and aggression due to serotonin-related deficits on the *cortical level*, causing detrimental effects in the top-down control or inhibition of behavior (Olvera, 2002). In sum, the inhibitory regulation of aggression is thought to emanate from serotonin (Siever, 2008). Consequently, if our hypothesis that high testosterone–low cortisol ratios predispose for social aggression in general is correct, low serotonin transmission in subjects with high testosterone–low cortisol ratios should potentiate reactive aggression.

The interactions between the steroid hormones cortisol and testosterone and the monoamine serotonin are not well understood. However, there is evidence for antagonistic effects of testosterone on the serotonergic system, and available evidence suggests that serotonin predisposes for reactive aggression under conditions of heightened testosterone (the testosterone–serotonin link; Birger et al., 2003; Delville, Mansour, & Ferris, 1996). Critically, Kubala, McGinnis, Anderson, and Lumia (2008) recently demonstrated that low serotonin can potentiate both fear and social aggression, but that testosterone blocks fear and enhances social aggression. In sum, low serotonin may add a fearful tendency to the aggression motives in subjects with high testosterone, combining to produce a more defensive–reactive form of aggression. Cortisol (corticosterone in animals), on the other hand, seems to augment the inhibition of aggression by increasing serotonergic function. Chronically elevated levels of cortisol generally inhibit aggression, but when cortisol levels are low, the function of serotonin is hindered, which may result in increased aggression (T. R. Summers et al., 2003). Indeed, animals with both chronically low corticosterone and serotonergic dysfunction show maladaptive, excessive forms of social aggression (C. H. Summers & Winberg, 2006). In the initial phase of aggressive attack, increases in cortisol and serotonin normally occur and are thought to be necessary to control and stop further attack. When the rise in

cortisol and serotonin does not occur, aggression endures and is much explosive and violent (T. R. Summers et al., 2003).

There is a thus a growing body of evidence showing that testosterone and cortisol, as well as testosterone and serotonin, may inhibit each other's biobehavioral actions (see also McEwen & Wingfield, 2003; Viau, 2002). Cortisol and serotonin, on the other hand, seem to have mutually agonistic properties in the context of aggressive behavior. Our proposed steroid hormone–monoamine profile for reactive aggression can therefore be reconciled with the neurobehavioral interactions of these chemicals as they are currently understood. In sum, a blend of high levels of testosterone, low levels of cortisol, and deficient serotonin function may well underlie the socially explosive mind. This concept lies at the core of our triple imbalance hypothesis (TIH) of reactive aggression.

THE TRIPLE BALANCE HYPOTHESIS

Before we turn to the TIH of reactive aggression, it is necessary to discuss its basic foundations and core underlying assumptions. These come from the triple balance hypothesis (TBH) (van Honk & Schutter, 2005, 2006b). According to the TBH, the well-being of social animals depends on their ability to respond to environmental rewards and punishments with socially appropriate approach- or withdrawal-related actions. A fine-tuned balance in approach- and withdrawal-related actions to punishments and rewards is critical for survival and signifies health for the individual and group (Ressler, 2004). Indeed, most of the emotional disorders—for example, social anxiety, depression, and extreme social aggression—can be conceptualized as imbalances in emotional approach and withdrawal (van Honk et al., 2005).

The TBH is a neuro-evolutionary psychobiological framework that elaborates on notions from neuroanatomy and biology as presented by Hughling Jackson (1887) as well as MacLean (1990) and theoretical frameworks from evolutionary perspectives, psychophysiology, psychology, and psychiatry (Porges, 2003). The fundamentals of the TBH are centered around three biobehavioral balances that subsequently evolved *in our evolutionary lineage*: reptiles, rodents, and primates/humans. Of the essence, reactive aggression in reptiles, rodents, and humans critically depends on the defense circuits of the brain, which involve the amygdala, hypothalamus,

and brainstem (Blair, 2004; Hermans et al., 2008). Importantly, in these circuits the HPA and HPG axes with their end products cortisol and testosterone play decisive differential roles in the predisposition and execution of fight or flight. Cortisol and testosterone are vitally accountable for the so-called *subcortical balance*. Moreover, these hormones also contribute importantly to set points and changes in communication between subcortical and cortical regions of the brain (Schutter & van Honk, 2004, 2005).

The TBH furthermore suggests that a rudimentary PFC that evolved 200 million years ago in early rodents provides for the beginnings of *cortical* top-down modulation of *subcortically* generated emotive drives strongly depending upon the *cortical–subcortical balance*. In primates and especially humans, social systems became much more complex, and the role of the PFC became larger and more centralized. The PFC increased in volume, and regional specialization in the form of lateralization occurred to fine-tune the avoidance–approach system to prevent conflict among action tendencies. In nonhuman primates, fear/avoidance circuitry is localized in the right prefrontal cortex (Kalin, Larson, Shelton, & Davidson, 1998) and aggression/approach circuitry is localized in the left prefrontal cortex (Harmon-Jones & Allen, 1998). This final balance, among the left and right prefrontal cortices, we term the *cortical balance*.

THE TRIPLE IMBALANCE HYPOTHESIS OF REACTIVE AGGRESSION

The TIH is presently applied to approach- and withdrawal-related features of social–emotive processing in human reactive aggression. As noted, the TBH postulates that evolution provided us with three gradually evolved, loosely coupled bipolar continua in affective reactivity that seek homeostasis (van Honk, Morgan, & Schutter, 2007). These are responsible for the flexibility and vulnerability of human adaptation. Importantly with respect to social aggression, the steroids cortisol and testosterone seem capable of inducing neurochemical changes advancing from the subcortical amygdala-centered level that influence the way in which organisms perceive and act in the presence of social threat. Exaggerated perceptions of hostility in others and aggressive responses to social threats can be observed in reactive aggressive individuals, suggesting a neuroendocrine pro-

file of heightened testosterone and lowered cortisol. In socially threatening encounters the facial expression of anger plays a pivotal role in humans. The angry face holds signaling properties that can modify and control the behavior of individuals and social groups. Whereas overt physical aggression establishes dominance–submission relationships in rodents, ritualized challenges based on anger displays generally establish the social hierarchy in humans without overt aggression occurring (Öhman, 1997; van Honk & Schutter, 2007). The angry facial expression serves as a threat signal in dominance encounters. Gazing longer at angry faces (vigilant response) indicates that the subject interprets the angry face as a dominance challenge and accepts this challenge (fight/approach response). Shorter gazing (gaze aversion) reflects submission, and the subject defuses further aggression (Mazur & Booth, 1998). Depending on the social relation between sender and receiver, angry faces can therefore be responded to with both fearful submission and aggressive dominance (van Honk & Schutter, 2007).

An extensive line of studies from our laboratory suggests that these vigilant and avoidant responses to angry facial expressions convey motives for aggressive dominance and fearful submission (reviewed in van Honk & de Haan, 2001, and van Honk & Schutter, 2007). This research, together with the data reviewed above (Mehta & Josephs, 2008; Pajer et al., 2006; Popma et al., 2007), provides strong evidence for the high testosterone–cortisol ratio hypothesis, and further predictions of the TIH model are discussed below. Note, however, that the TIH is a comprehensive and somewhat ambitious one. Thus, although we review quite a bit of evidence in support of aspects of the model, the model also points to productive potential in areas of inquiry as yet not addressed.

SUBCORTICAL IMBALANCE HYPOTHESIS

To begin with, we found that both high testosterone levels and low cortisol levels predicted more vigilant responses to angry facial expressions in an emotional Stroop task (van Honk et al., 1998, 1999, 2000). It was argued that these findings indicate that both high levels of testosterone and low levels of cortisol predispose for aggressive or approach-related responses to angry facial expressions. This would be in agreement with known relations between high testosterone and

aggressive, dominating personality styles and between low cortisol and socially aggressive dispositions (van Honk & Schutter, 2006b). We next sought direct evidence for a role of testosterone in social aggression by administering the hormone in healthy young women. The dependent variable was the cardiac defense response: An acceleration of heart beat within 5 seconds after stimulus presentation was thought to signal flight-fight preparation (Öhman, 1997). It was hypothesized that testosterone would induce cardiac acceleration in response to threatening faces. In a double-blind placebo-controlled design, healthy young women passively viewed neutral, happy, or angry faces. Testosterone induced a significant increase in the cardiac defense reflex for the angry face condition but not the other two face conditions. We argued that, given the fear-reducing properties of testosterone (Hermans et al., 2006; van Honk et al., 2005), this cardiac acceleration induced by testosterone indicates enhanced predisposition to react with aggression, rather than fear, to social threats (van Honk et al., 2001).

These data (van Honk et al., 2001) are consistent with correlational evidence for relations between testosterone and vigilant responses to angry facial expressions (van Honk et al., 1999; Wirth & Schultheiss, 2007). However, the data do not provide information on the neural mechanisms involved. Crucially, it is known that testosterone influences affective responsivity by binding to specific steroid-responsive receptors in limbic system networks (Wood, 1996). A key element in these networks is the amygdala. The central nucleus of the amygdala, directly and indirectly via the hypothalamus, innervates brainstem heart rate control centers. Note that there is evidence of amygdala–hypothalamus–brainstem circuits mediating reactive aggression in rodents, and neuroimaging studies have indicated a key role of the amygdala in autonomic responsiveness to angry faces in humans (Domes et al., 2007; Morris, Öhman, & Dolan, 1999).

Following this line of evidence, we recently used a passive viewing design with emotional facial expressions during functional magnetic resonance imaging (fMRI). In this study, the amygdala, hypothalamus, and brainstem were among the regions of interest (Hermans et al., 2008). In the first part of the study (Hermans et al., 2008), 12 female participants underwent fMRI while passively viewing angry and happy facial expressions. Results showed activation to angry facial expressions (using happy faces as contrast) in the amygdala, hypothalamus, and brainstem as well as in the orbitofrontal cortex

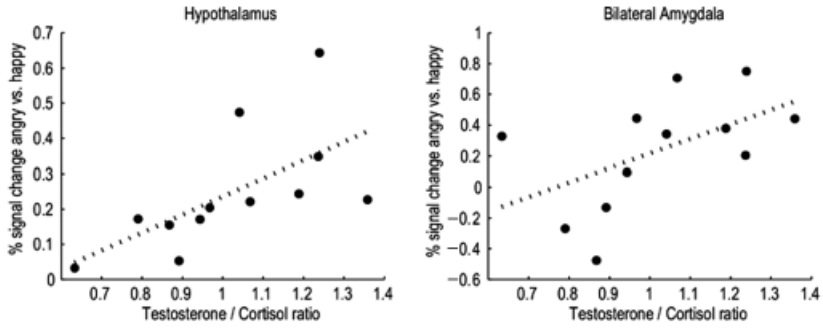

Figure 1
Scatterplots of the correlation between testosterone/cortisol ratio and the average magnitude of the blood oxygen level–dependent response to angry versus happy facial expressions in the hypothalamus and the amygdala (Hermans et al., 2008).

(Brodmann area 47), which is strongly implicated in the regulation of human social aggression (Blair, 2003, 2004). Most importantly with respect to our model, cortisol and testosterone were also measured from saliva during the experiment. The high testosterone–cortisol ratio was determined and correlations were computed over regions of interest—amygdala, hypothalamus, brainstem, and orbitofrontal cortex. As shown in Figure 1, high testosterone–cortisol ratios predicted significant neural activation of the hypothalamus and right amygdala in response to angry facial expressions. This adds evidence to our suggestion of the role of the high testosterone–low cortisol ratio in social aggression, as the hypothalamus and the amygdala are considered part of the subcortical reactive aggression circuit (Blair, 2004).

The second part of the Hermans et al. (2008) study was a placebo-controlled experiment that revealed significantly enhanced activation of the subcortical reactive aggression network (i.e., the amygdala, hypothalamus, and brainstem) in response to angry faces after the administration of testosterone. In sum, the data of Hermans and colleagues are in line with findings on testosterone and responsivity to angry facial expressions (e.g., van Honk et al., 1999, 2001; Wirth & Schultheiss, 2007) and concur with animal research by demonstrating that testosterone increases activity in subcortical neural circuits of social aggression in response to threat.

However, these data (Hermans et al., 2008) seem difficult to reconcile with data showing that reactive aggressive patients (patients

with intermitted explosive disorder [IED]) have difficulties in the conscious recognition of angry facial expressions (Best, Williams, & Coccaro, 2002). Given our findings on testosterone and angry facial expressions, impaired recognition of anger in aggressive individuals seems counterintuitive in our model (Hermans et al., 2008; van Honk et al., 1998, 1999, 2001). It might, however, be argued that conscious anger recognition acts at explicit, higher levels of processing, and our data linking testosterone to vigilant responses to angry facial expressions concern lower implicit processing levels (cf. Toates, 2006). Indeed, Blair (2003) has suggested that impairments in facial anger recognition may mediate socially aggressive subjects' failure to respond to social correction signals. The facial signal of anger on higher processing levels thus facilitates the functioning of social systems through its socially corrective properties (Blair, 2003).

Strong support for the implicit–conscious processing distinction would be gained if testosterone were to impair the conscious recognition of facial anger. This hypothesis was tested in a double-blind, placebo-controlled, within-subjects testosterone administration design (van Honk & Schutter, 2007). An emotion recognition task was administered to measure the conscious recognition of threatening (fear, anger, and disgust) and nonthreatening (happiness, sadness, and surprise) facial expressions. Because real-life facial expressions are dynamic, gradually morphed instead of static images of emotional expressions were used to increase of ecological validity. The experiment measured recognition sensitivity as the percentile of intensity at which a subject is able to correctly identify an emotional facial expression. The sensitivity threshold was defined as the morphing percentage at which the emotion is consistently correctly recognized. Testosterone induced an overall reduction in the conscious recognition of facial threat. Importantly, however, separate analyses for the three categories of threat faces indicated that this effect was most pronounced for angry facial expressions. In summary, testosterone augments physiological and cognitive–affective responses to angry facial expressions (van Honk et al., 1999, 2001) and increases activity in the brain structures critically involved in reactive aggressive responses—that is, the amygdala, hypothalamus, and brainstem (Hermans et al., 2008). On the other hand, testosterone impairs the conscious recognition of anger. We sought to explain this dissociation in terms of implicit and explicit information processing mechanisms following Toates (2006), but how can the

dissociation be explained in terms of the brain mechanisms involved? We pursue this question below.

CORTICAL-SUBCORTICAL IMBALANCE HYPOTHESIS

Importantly, steroid hormones can influence social brain processing not only locally—for example, by inducing peptide synthesis—but also by way of modulating brain communication. Cross-frequency analyses may provide an index for cortical–subcortical coupling in the human electroencephalogram (EEG; Schutter, Leitner, Kenemans, & van Honk, 2006), and recently evidence was found that testosterone decreases the coupling between subcortical and cortical regions (Schutter & van Honk, 2004). Cortical–subcortical coupling is of vital importance for top-down cognitive control over social-aggressive tendencies (Kringelbach & Rolls, 2003; Reiman, 1997; van Honk et al., 2005). Cortical–subcortical coupling, however, also mediates bottom-up transmission of information conveying angry threat value, rapidly detected by the amygdala (Morris et al., 1999), to the orbitofrontal cortex where higher-level modulation of emotion occurs (Reiman, 1997; van Honk et al., 2005). In support of the testosterone–cortisol ratio hypothesis, increased levels of cortisol are accompanied by increased cortical–subcortical coupling (Schutter & van Honk, 2005). As can be seen from Figure 2, this pattern stands in direct contrast to the effects of high levels of testosterone (Schutter & van Honk, 2004).

Thus a feasible neurobiological mechanism for the observed testosterone-induced reductions in the conscious recognition of angry facial expressions is the testosterone-induced reduction in cortical–subcortical coupling (Schutter & van Honk, 2004), which impedes information transfer between the amygdala and orbitofrontal cortex. Subcortical activation in aggression circuits in combination with reduced cortical–subcortical coupling constitutes a neurobiologically realistic two-layered mechanism whereby testosterone predisposes individuals for social aggression. Critical evidence for impaired cortical–subcortical coupling in reactive aggression comes from IED patients in an fMRI experiment of Coccaro, McCloskey, Fitzgerald, and Phan (2007). These researchers show that, unlike control subjects, these patients fail to demonstrate subcortical–cortical (i.e., amygdala–orbitofrontal cortex) coupling during displays of angry faces. As noted, subcortical responses to social threat signals (angry

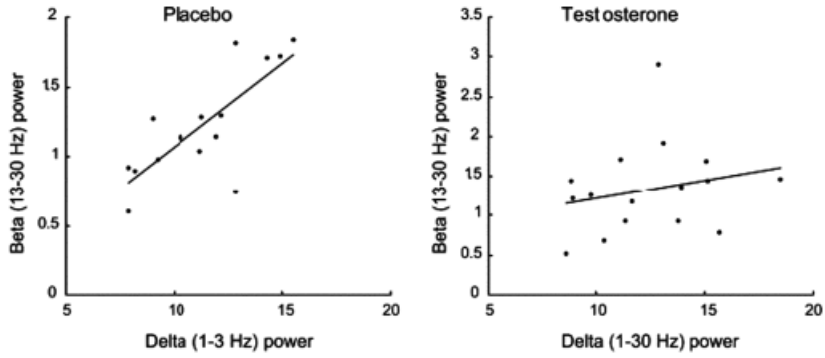

Figure 2
Decoupling of subcortical–cortical communication: Significant loss of midfrontal delta–beta coupling after testosterone compared to placebo administration in healthy human volunteers (Schutter & van Honk, 2004).

facial expressions) can be modulated on cortical levels (van Honk & Schutter, 2007), but in these IED patients it seems that subcortical–cortical interactions are dysfunctional and this may well underlie their reactive aggression tendencies.

Human brain studies have provided evidence for the involvement of the PFC in aggression (Davidson, Putnam, & Larson, 2000). Neuropsychological studies have shown that damage to the PFC often results in impulsive aggression (Damasio, 1994). Also, reduced gray matter density in the PFC of aggressive individuals diagnosed with antisocial personality disorder has been demonstrated (Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000). Neurological and neuroimaging studies of aggression indicate a critical role of the orbitofrontal cortex, which has dense connections to the amygdala (Blair, 2004; Coccaro et al., 2007; Hermans et al., 2008). This connectivity is crucial in cortical–subcortical communication, and thus is at least partly under control of the hormones testosterone and cortisol (Schutter & van Honk, 2004, 2005). However, there is another broad-spectrum property of the PFC that is less constrained by bottom-up influences such as those involving testosterone and cortisol. As indicated next, the *cortical imbalance* concept captures an important aspect of motivation and, by extension, social aggression likelihood.

CORTICAL IMBALANCE HYPOTHESIS

Evolution has equipped human primates with three gradually evolved, bipolar continua in affective reactivity. The upper layer is a cortical balance and most strongly involves transitions from hormone-driven affective-reflexive behavior to more cognitive-driven reflective behavior (Curley & Keverne, 2005). For better or for worse, humans are, to a degree, able to master their hormonal drives (cf. Hauser, 2007). Nonetheless, control mechanisms for regulating the balance between aggressive approach and fearful avoidance exist at the cortical level, as demonstrated by evidence for the frontal lateralization of motivational direction (Harmon-Jones, 2003, 2004). This lateralization probably helps to prevent conflict among the action tendencies of approach and withdrawal and so enhances functional capacities and efficiencies for this reason (Davidson, 2004).

The measurement of frontal brain asymmetries by EEG has proven to be a good starting point to address issues concerning individual differences in cerebral dominance and the propensity to engage in aggressive behavior. Left-sided dominance of resting state frontal brain activity in the healthy human brain has proven to be predictive for increased behavioral approach and reward dependency (Schutter, de Haan, & van Honk, 2004). Furthermore, naturally occurring cerebral asymmetries in frontal activity correlate with individual differences in approach- and withdrawal-related behavioral tendencies (Schutter, de Weijer, Meuwese, Morgan, & van Honk, 2008). An increasingly influential theory is the motivational direction model (Harmon-Jones, 2003, 2004; see Carver & Harmon-Jones, 2009). EEG studies have demonstrated left frontal cortex activation in anger and aggression provocation paradigms (Harmon-Jones, 2003; Harmon-Jones & Sigelman, 2001). Trait anger seems to be a strong predictor for reactive aggression (Wilkowski & Robinson, this issue). This would agree with the TIH cortical balance perspective. In this connection, Harmon-Jones and Allen (1998) found that trait anger predicted increased left frontal activity and decreased right frontal activity (as assessed by the A. H. Buss & Perry, 1992, anger scale). Hewig, Hagemann, Seifert, Naumann, and Bartussek (2006) replicated these effects using the Anger-Out scale from the State–Trait Anger Expression Questionnaire (STAXI; Spielberger, 1988), which was designed to assess approach-motivated anger. In an important extension of this work, Rybak, Crayton, Young,

Herba, and Konopka (2006) found that among adolescent male psychiatric patients, more symptoms of aggression and impulsivity related to greater relative left frontal activity.

To address the limitations of the above correlational studies, experiments have been conducted in which anger is manipulated and the corresponding effects on regional brain activity are examined. In Harmon-Jones and Sigelman (2001), participants were randomly assigned to a condition in which they were insulted or treated in a neutral manner by another ostensible participant. Immediately following the treatment, EEG data were collected. As predicted, individuals who were insulted showed greater relative left frontal activity than did individuals who were not insulted. Additional analyses revealed that within the insult condition, self-reported anger and aggression were positively correlated with relative left frontal activity. Neither of these correlations was significant in the no-insult condition. These results suggest that relative left frontal activation was associated with the evocation and experience of anger. This research provided the first demonstration of a relationship between state anger and relative left frontal activation.

The studies discussed above provide evidence that anger and aggression are commonly associated with an increase in left frontal cortical activity, suggesting that such activity is associated with approach motivation (note that this set of findings contradicts valence models of prefrontal asymmetry; Carver & Harmon-Jones, 2009). If this association is causal, the converse should also follow: Increases in left frontal cortical activity should be associated with increases in anger and aggression. One way to manipulate frontal asymmetry is unilateral hand contractions. A recent experiment (Peterson, Shackman, & Harmon-Jones, 2008) manipulated asymmetry in this way. Compared to participants who contracted their left hand, participants who contracted their right hand evidenced greater relative left cortical activation over central and frontal regions. Moreover, as compared to left-hand contraction participants, those who contracted their right hand delivered longer and louder noise blasts to their opponent, a well-validated behavioral model of reactive aggression. This manipulation of brain asymmetry and its effect on aggressive behavior provides strong evidence for the theory of left PFC dominance in aggression.

However, if one could physiologically manipulate brain asymmetry, this might provide even stronger evidence for direct connections

(Harmon-Jones, 2003). A technique called transcranial magnetic stimulation (TMS) seems able to shift the frontal cortex asymmetry depending on stimulation parameters (Schutter, van Honk, & Panksepp, 2004). TMS is a method that exploits the principle of electromagnetic induction. When TMS is applied continuously for a prolonged period of time, for instance, one pulse per second (1 Hz) for 20 minutes (1200 pulses), it is called repetitive TMS (rTMS). Physiological studies on the frontal cortex have demonstrated that this procedure locally decreases neural excitability (Pascual-Leone, Bartres-Faz, & Keenan, 1999). In addition to these local effects that result directly from the magnetic pulse, distal effects are also observed as a result of neural interconnectivity (Wassermann, Wedegaertner, Ziemann, George, & Chen, 1998).

In the first rTMS experiment dealing with the lateralized role of the PFC in anger, 1-Hz rTMS was applied continuously for 20 minutes over the left and the right prefrontal cortex, and emotional responses to angry facial expressions were investigated (d'Alfonso, van Honk, Hermans, Postma, & de Haan, 2000). Results indicated that reducing cortical excitability of the right PFC causes emotionally vigilant responses to angry facial expressions, whereas reducing cortical excitability of the left PFC causes emotionally avoidant responses to angry facial expressions. Moreover, additional analyses on sympathetic and parasympathetic activity of the heart demonstrated that the vigilant responses to angry facial expressions after right compared to left PFC rTMS was significantly correlated with higher levels of sympathetic activity (van Honk, Hermans, D'Alfonso, et al., 2002). These findings concur with an extensive line of research showing that the approach-related emotions (i.e., anger) are processed by the left PFC and avoidance-related emotions by the right PFC (Harmon-Jones, 2003).

In a follow-up study, emotional responses to fearful facial expressions were investigated following 1-Hz rTMS to the right PFC and compared to sham rTMS (van Honk, Schutter, D'Alfonso, Kessels, & de Haan, 2002). In concordance with the motivation direction model, reducing right PFC excitability resulted in a significant decrease in vigilant responses to fearful facial expressions. This lack of attention to the fearful danger signal seems a risky behavioral strategy, most likely to be observed in low anxious, anger-prone, and thus left PFC dominant individuals. Indeed, empirical proof for a right PFC induced contralateral increase in left PFC excitability was pro-

vided by electrophysiological recordings (Schutter, van Honk, d'Alfonso, Postma, & de Haan, 2001). Moreover, in addition to these left-sided increases in frontal activity after 1-Hz rTMS over the right PFC, significant decreases in self-reported anxiety were found. Finally, when returning to the use of angry facial expressions as target stimuli in another 1-Hz rTMS study, significant reductions in attentionally modulated memory for angry faces were shown after reducing left PFC excitability. In this study, TMS intensity parameter settings were set low in an attempt to induce more limited, unilateral effects (Gerschlager, Siebner, & Rothwell, 2001). Indeed, as can be seen from Figure 3, neither sham nor right PFC 1-Hz rTMS stimulation had influence on the processing of facial anger (van Honk & Schutter, 2006a).

In sum, this series of TMS modulation studies provides a plausible neurobiological basis for a close link between frontal cortical asymmetries (i.e., cortical imbalance) and aggression-related behavior and strongly support the theoretical model of Harmon-Jones (2003, 2004). Rather than being solely a method for the modulation of cortical brain asymmetries, TMS can also be deployed to measure resting state cortical excitability and explore interrelations between frontal asymmetries and emotional tendencies for approach- and avoidance-related behavior. Cortical excitability can be conceptualized as the minimum intensity needed to activate pyramidal neurons in the primary motor cortex with TMS, as assessed in terms of hand muscle contractions (Hallett, 2007). Higher levels of cortical excitability during resting conditions would be linked to lower activation thresholds for environmental stimulation and thus be of possible use in assessing a neural diathesis of threat-related reactivity.

In this connection, measuring cortical excitability during a resting condition may provide a way of quantifying aspects of "cortical brain states" associated with individual differences in personality traits and related motivational tendencies. Indeed, in a recent study, cortical excitability of the left and right primary motor cortex was determined in 24 young healthy right-handed volunteers. This led to the computation of a cortical excitability asymmetry index (Schutter, de Weijer, et al., 2008). The aim of the study was to seek evidence for whether an asymmetry in cortical excitability would predict emotional approach or emotional avoidance as indexed by the BIS/BAS questionnaire (Carver & White, 1994). In line with the cortical-centered model of frontal asymmetry, relatively higher left-sided

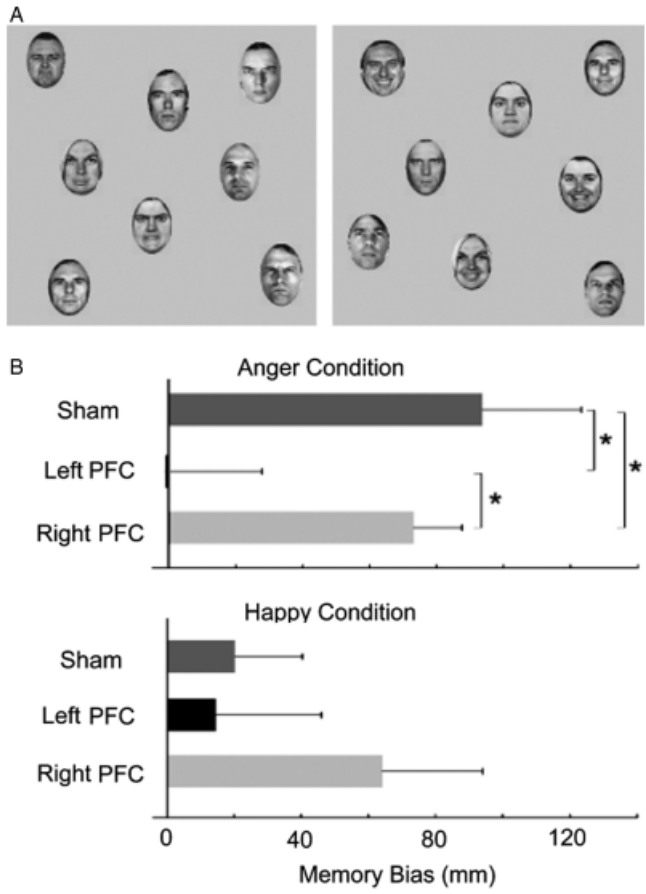

Figure 3
Displays used in the memory task (A) and results (B). On each trial, a display of angry and neutral faces or a display of happy and neutral faces was presented for 30 seconds. The graphs show memory bias after repetitive transcranial magnetic stimulation (rTMS) of left prefrontal cortex (PFC) and right PFC and after sham rTMS. Asterisks indicate significant differences between conditions (van Honk & Schutter, 2007).

cortical excitability levels were associated with enhanced emotional approach relative to emotional avoidance. This result has been conceptually replicated in a study that assessed the coherence between left motor cortex and left PFC, and observed that more coherence between these regions directly related to individual differences in

approach motivation (Peterson & Harmon-Jones, 2008). In conclusion, a left-sided cortical asymmetry is associated with increased behavioral approach and anger and paralleled by reduced behavioral withdrawal and increased anxiety. It is proposed that an extreme left-sided cortical imbalance reflects a motivational state of readiness to respond to social threat with anger and aggression rather than fear and submission.

Some further evidence suggests that frontal asymmetry is related to cortisol levels. That is, right-sided frontal asymmetry has been associated with cortisol, but these relationships have only been found in primates and children (K. A. Buss et al., 2003; Kalin et al., 1998) and not yet in human adults. The relationship of testosterone and frontal asymmetry has not been established. Although absence of evidence, of course, does not directly imply evidence of absence, this gives provisional support to our notion that the cortical balance, to an extent, escapes the hormonal constraints of the subcortical balance. Human reactive aggression, consequently, is more complex than reactive aggression as found in reptiles or rodents.

CONCLUSION

We proposed that hormonal imbalances induce motivational imbalances on, and between, the subcortical and cortical levels of the brain. In social aggression, this hormonal imbalance consists of relative high levels of testosterone against low levels of cortisol, basically resulting from lowered activity of the HPA versus HPG systems. The high testosterone–cortisol ratio creates a primal motivational stance favoring reward–approach over punishment–withdrawal. It also appears to reduce cortical–subcortical coupling, depriving the individual of the subcortical input thought to be critical in guiding behavior in socially and morally appropriate fashions (Blair, 2003; Hauser, 2007). Serotonin may also play a role in the model, and Figure 4 presents a graphic summary of some TIH mechanisms and their interactions.

The notion that high testosterone–cortisol ratios together with low central serotonin transmission predispose one toward reactive aggression brings together several lines of animal and human research, including many techniques and methods. Still, although the relation between low central serotonin transmission and reactive aggression is established throughout many species, low serotonin has been impli-

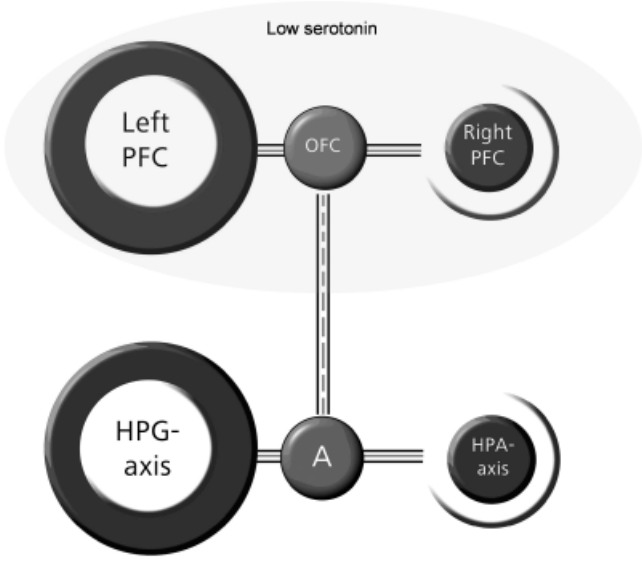

Figure 4
The triple imbalance hypothesis (TIH) of reactive aggression. Hyperactivation of the hypothalamic pituitary gonadal axis (HPG) or/and hypoactivation of the hypothalamic–pituitary–adrenal axis (HPA) results in a high testosterone–cortisol ratio. This sets the *subcortical system* in a reward-driven aggressive mode and reduces cortical–subcortical cross talk, especially between the orbitofrontal cortex (OFC) and the amygdala (A). The hormonal imbalance may also partly underlie deficient serotonergic function at the cortical level.

cated in diverse phenomena related to emotional impulsivity. Thus a crucial next step is to investigate the proposed role of testosterone and cortisol in understanding serotonin's effects. For example, low serotonin may promote aggression for those with a high testosterone–cortisol ratio but anxiety for those with a low testosterone–cortisol ratio.

Nonetheless, the TIH may serve as a framework for elucidating the psychological and biological antecedents of reactive aggression and when further developed clinical applications can be envisioned. For instance, the standard method of diagnosis by observation and interview could be supplemented with, and compared to, a neurobiological measurement of salivary testosterone, cortisol, and their relative balance. Furthermore, EEG recordings might be of diagnostic value as well. When imbalances are observed

on one or several levels, they, in theory, could be restored by hormone or/and serotonin intervention. Cognitive–emotive therapies may also have importance in restoring and/or promoting cortical balance. In sum, the TIH of reactive aggression might act as a heuristic framework pointing to multiple ways whereby imbalances occur and in which biologically informed diagnoses and interventions can be developed.

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