


act aggressively in response to perceived threats and when seeking rewarding stimuli (van Honk et al., 2010). Then we review recent research on reactive aggression which discusses the role that each of the three brain systems have in motivating and facilitating reactive aggression. Finally, we discuss evidence for the role of the corpus callosum in mediating imbalances in the most recently evolved of these brain systems.

Core Brain Chemicals for Reactive Aggression

A promising approach to modeling neuro-endocrine contributions to anger and reactive aggression in humans has focused on the mutually antagonistic effects of testosterone and cortisol (van Honk et al., 2010). In non-human species, testosterone levels are reliably associated with increased aggression toward conspecifics, and they predict sex differences in socially aggressive behavior (Archer, 1988). In humans, greater testosterone levels have been found to predict aggressive attitudes, with castration reducing their endorsement (Van Goozen, Cohen-Kettenis, Gooren, Frijda, & Van De Poll, 1995). Moreover, situationally increased testosterone levels in response to a laboratory anger induction predict increased self-reported anger to the induction (Peterson & Harmon-Jones, 2012). Additional evidence for the role of testosterone in shaping anger and aggressive behavior in humans comes from a program of research associating testosterone levels with observer-rated violence and aggressive antisocial behavior in male and female prison populations (Dabbs, Carr, Frady, & Riad, 1995; Dabbs & Hargrove, 1997; Dabbs & Morris, 1990). Intriguingly, because of the putative mechanism by which testosterone affects aggression, its effects may not be consciously accessible or observed in self-report (Van Honk & Schutter, 2007a). In contrast to testosterone, cortisol has been associated with a reduced tendency to engage in aggressive behaviors. Lower levels of cortisol are observed in populations at risk of violent antisocial outbursts and children with socialization problems (McBurnett et al., 1991; Vanyukov et al., 1993).

Several properties of the endocrine axes that produce testosterone and cortisol are of particular importance with respect to their role in motivating and guiding aggressive behavior. First, the hypothalamic–pituitary–gonadal (HPG) and hypothalamic–pituitary–adrenal (HPA) axes—which synthesize testosterone and cortisol respectively—are mutually antagonistic (Viau, 2002). Testosterone has been shown to inhibit stress-related responses in the HPA (Viau, 2002), while cortisol—and its analogues in other mammals—has been shown to inhibit the release of testosterone and the action of testosterone at target sites (Johnson, Kamilaris, Chrousos, & Gold, 1992; Tilbrook, Turner, & Clarke, 2000). Second, testosterone and cortisol have distinct effects on the amygdala, with the former promoting vasopressin gene expression and approach behaviors (Schulkin, 2003), and the latter promoting corticotropin releasing hormone (CRH) gene expression and withdrawal behaviors (Schulkin, 2007).

The opposing effects of testosterone and cortisol are also observed at a psychobiological level in many species. Testosterone has been found to increase approach behavior, including aggression and reward sensitivity (Carr, Führer, & Phillips, 1989), while also reducing withdrawal behaviors, fear, and punishment sensitivity (Hermans, Putman, Baas, Koppeschaar, & Van Honk, 2006). Research using the Iowa Gambling Task (Bechara, Damasio, A. R., Damasio, H., & Anderson, 1994) has found testosterone administration to increase sensitivity to reward, causing individuals to make more risky and disadvantageous choices (Van Honk et al., 2004). Correlational findings suggest that cortisol has the opposite effect, with more advantageous choices made by individuals with high cortisol levels, and more disadvantageous choices made by individuals with low cortisol levels (Van Honk, Schutter, Hermans, & Putman, 2003).

Rather than either one of these hormones being singularly responsible for aggressive tendencies, the imbalance between testosterone and cortisol is pivotal (van Honk et al., 2010). The findings of several studies that included measures of both testosterone and cortisol are particularly revealing, and provide critical support for this hypothesis. First, overt aggression in adolescent males is predicted by high testosterone only in those who also have low cortisol levels (Popma et al., 2007). Second, girls with conduct disorder have been found to have greater testosterone and lower cortisol levels (Pajer et al., 2006). Third, research examining the contributions of testosterone and cortisol to reactive aggression and dominance indicated that testosterone predicted increased aggression in males and females, but only in those with low cortisol. High levels of cortisol may even reverse the effects of testosterone, with less aggression and dominance observed in high-cortisol, high-testosterone subjects (Mehta & Josephs, 2010).

Interestingly, both proactive and reactive aggression have been associated with basal testosterone and cortisol levels in opposite ways, and there is evidence that the monoamine serotonin is particularly important for distinguishing between these aggression subtypes (van Honk & Schutter, 2006a). Low serotonin levels in individuals with high testosterone and low cortisol levels may predict their proclivity to respond with reactive aggression (Miezczak et al., 2007).

Although the mechanisms that link serotonin and the steroid hormones testosterone and cortisol are not well understood, there is abundant evidence for the existence of bidirectional relationships between serotonin and the steroid hormones testosterone and cortisol. Testosterone has antagonistic effects on serotonergic function, while low serotonin appears to predispose individuals toward reactive aggression in high testosterone contexts (Birger et al., 2003). Although low serotonin enhances withdrawal- and approach-related behaviors—fear and social aggression—testosterone blocks the effect of the former (Kubala, McGinnis, Anderson, & Luminà, 2008). Low serotonin
may shift aggression-related motivations toward a fearful-defensive form of reactive aggression (van Honk et al., 2010). Interestingly, cortisol and its analogues differentially augment the inhibitory effects of serotonin. While high cortisol levels are associated with reduced aggression, low levels are associated with a dampening of serotonin function, and increased aggression in response to stress (C. H. Summers & Winberg, 2006; T. R. Summers et al., 2003). During stress-related aggressive acts, increased cortisol and serotonin levels serve to inhibit the escalation of further aggression; when the cortisol and serotonin response does not occur, aggressive acts are longer and more intense (T. R. Summers et al., 2003).

### The Triple Balance Hypothesis

Before discussing the Triple Imbalance Hypothesis and supporting research, it is necessary to detail its conceptual and theoretical foundations and core assumptions. These are primarily derived from the Triple Balance Hypothesis (TBH), which proposes that the survival and well-being of social animals is dependent on the selection of appropriate responses to rewarding and punishing features of their environment (van Honk & Schutter, 2005, 2006b). These responses can be conceptualized as being either approach- or withdrawal-related actions, and a balance between these different motivational directions is critical for the well-being of individuals and groups (Ressler, 2004).

Building on previous neuroanatomical and biological frameworks and theories that utilize an evolutionary approach to explaining their respective phenomena (Jackson, 1887; MacLean, 1990), the TBH is organized into three interacting and phylogenetically distinct biobehavioral balances. The oldest level of this model is the *subcortical balance*, wherein testosterone and cortisol shape approach- and withdrawal-related actions and facilitate their execution (van Honk et al., 2010). Moreover, testosterone and cortisol have differential effects on behavior and on subcortical regions that comprise the brain’s defense circuits (e.g., the amygdala, hypothalamus, and brain stem; Blair, 2004; Hermans, Ramsey, & van Honk, 2008).

The next most recent level is the top-down cortical control of subcortical regions via the prefrontal cortex (PFC). The evolution of the PFC—beginning approximately 200 million years ago—allowed for the regulation of subcortical drives by the increasingly complex PFC, with the degree of regulation depending on *subcortical-cortical* balance.

Finally, in humans and non-human primates, the PFC has become increasingly specialized, with systems associated with approach- and withdrawal-related processes lateralized to the left and right hemispheres (Harmon-Jones & Allen, 1998; Hortensius, Schutter, & Harmon-Jones, 2012; Kalin, Larson, Shelton, & Davidson, 1998). These often competing and mutually inhibiting systems in the left and right PFC constitute the *cortical balance*.

### The Triple Imbalance Hypothesis

The Triple Imbalance Hypothesis (TIH) is focused on the three interacting and phylogenetically distinct brain systems that motivate and facilitate moving toward or moving away from stimuli as proposed in the TBH (van Honk et al., 2010). These systems are thought to underpin flexible and adaptive responding in contexts that may require approach-related (anger and aggression) or withdrawal-related (fear and submission) responses. The TIH posits that imbalances in these systems are predictive of an increased or decreased tendency to engage in reactive social aggression. Testosterone and cortisol have powerful neurochemical effects that progress from their subcortical amygdala-centered sites of action and influence the perception of and response to potential threats. In this context, the unconscious perception and evaluation of facial expressions of anger is of particular importance. In humans, angry faces serve as threat signals in social dominance contexts, with extended gaze and eye contact (e.g., vigilance) indicating that the facial expression is automatically evaluated as a dominance challenge, and expressing a willingness to confront this challenge. In contrast, rapidly averting one’s gaze is submissive, de-escalating aggression between both parties (Mazur & Booth, 1998). That is, angry faces can produce either an aggressive dominance response or a fearful submission response in individuals (van Honk et al., 2010; van Honk & Schutter, 2007a).

The extent to which these vigilance and avoidance responses reflect dominance and submission motivations, their relationship with other aggressive tendencies, and their subcortical and cortical underpinnings have been examined in a program of research. This research, and assumptions regarding the automatic evaluation of angry faces, forms the basis of empirical tests of the TIH. Below, we review evidence regarding imbalances at each level of the TIH.

### Subcortical Imbalances

Evidence for a subcortical imbalance model of reactive aggression came from early studies which showed that a high testosterone and low cortisol ratio was correlated with increased vigilance toward angry faces in emotional Stroop tasks (van Honk et al., 1998, 2000; van Honk et al., 1999). As noted above, increased vigilance toward angry faces is thought to reflect an approach-related and aggressive dominance response, an interpretation that is consistent with past research showing that high testosterone is associated with socially dominant attitudes and low cortisol with anti-social attitudes (van Honk & Schutter, 2006b).

There is also direct evidence for the enhancing effect of testosterone on social aggression. In a double-blind placebo-controlled study, young female participants passively viewed faces with angry, happy, or neutral expressions while pulse rate was measured via finger plethysmograph. These pulse data
were used to quantify the cardiac defense response (CDR), a phasic stimulus-driven increase in heart rate indicating preparation of flight or fight (Ohman, 1997). Testosterone administration was associated with greater CDR in response to angry faces, but not to happy or neutral faces (van Honk et al., 2001). Because testosterone inhibits fear and avoidance responses, the CDR potentiation defensibly reflects an increased tendency to respond to angry faces with dominance and aggression (Hermans et al., 2006; van Honk, Peper, & Schutter, 2005).

Recent research suggests that the aggression-enhancing and fear-reducing effects of testosterone may have two distinct neurochemical mechanisms (Terburg & van Honk, 2013). Although past studies have shown testosterone administration increases the blood-oxygen-level-dependent (BOLD) signal in regions that comprise the subcortical reactive aggression system (Blair, 2004; Hermans et al., 2008), recent research suggests greater specificity in the neurochemical mechanisms and behavioral consequences at the level of the amygdala. In addition to increasing aggressive vigilance via the upregulation of vasopressin gene expression in the central-medial amygdala (CMA), testosterone may also increase the inhibition of fear vigilance via more ventral regions of the amygdala like the basolateral amygdala (BLA). Recent studies suggest that lesions to the BLA are associated with enhanced vigilance toward faces expressing fear (Terburg, Morgan, et al., 2012), and increased attention toward frightened body postures (De Gelder et al., 2014). Using the same experimental model, testosterone administration has indeed been found to decrease vigilance to faces expressing fear (van Honk et al., 2005).

Importantly, the effects of testosterone on social aggression and dominance responses occur without conscious awareness, without voluntary control of aggressive behavior, and without subjective feelings associated with approach motivation. Instead, the enhancement of threat perception and motivation to respond with aggression by testosterone is non-conscious and automatic (van Honk et al., 2005). Previous studies have reported that patients with extreme, uncontrollable outbursts of reactive aggression (Intermittent Explosive Disorder [IED]) have difficulty consciously recognizing angry facial expressions (Best, Williams, & Coccaro, 2002), a finding that seems at odds with the vigilance-enhancing effects observed elsewhere (van Honk et al., 1999). Testosterone appears to inhibit the conscious recognition of anger (van Honk & Schutter, 2007a), while enhancing non-conscious reactivity and dominance-related behaviors. Empirical support for the unconscious-conscious distinction also comes from recent studies examining the effect of testosterone administration on gaze fixation and saccade latencies away from eye contact with angry faces (Terburg, Aarts, & van Honk, 2012). Unlike previous emotional Stroop tasks, which required participants to name the color of each stimulus (e.g., van Honk et al., 1998, 2000; van Honk et al., 1999), the eye-tracked gaze aversion task requires participants to use saccades away from the eye region of the face stimuli to indicate their response (Terburg, Aarts, et al., 2012; Terburg, Hooveld, Aarts, Kenemans, & van Honk, 2011), with more rapid saccades reflecting enhanced gaze aversion. Administration of testosterone was found to reduce gaze aversion from angry faces, with greater saccade latencies compared to participants given a placebo. Moreover, the administration of testosterone did not influence participants’ subjective sense of dominance or aggression (Terburg, Aarts, et al., 2012). Previous research has also found that saccade latencies are related to self-reported dominance (as assessed by the drive and reward-seeking subscales of the BAS; Carver & White, 1994), suggesting that the eye-tracked gaze aversion task provides an index of dominance motivations (Terburg et al., 2011). Importantly, recent work shows that dominance motivation is only associated with gaze aversion when the emotional content of stimuli is successfully masked, supporting the interpretation that these processes are unconscious and automatic (Hortensius, van Honk, de Gelder, & Terburg, 2014).

Although testosterone-cortisol imbalances do appear to produce quite different effects on unconscious and conscious aggression-related processes, can this be understood in terms of the brain mechanisms responsible? We discuss this question below.

### Cortical–Subcortical Imbalances

The influence of testosterone and cortisol on the processing of motivationally relevant stimuli occurs at multiple levels. Not only do these steroid hormones modulate activity at subcortical levels (e.g., in the amygdala), but they also alter communication between subcortical and cortical regions, which may give rise to differences in the processing of angry faces and in the regulation or dysregulation of reactive aggression actions. The bidirectional coupling between key subcortical and cortical regions is instrumental for the top-down cognitive regulation behavior (Kringelbach & Rolls, 2003; Reiman, 1997; van Honk et al., 2005), as well as the rapid feeding forward of bottom-up impulses from the subcortex (Morris, Ohman, & Dolan, 1999). In particular, the rapid processing of socially threatening stimuli by the amygdala may be fed forward to the orbital frontal cortex (OFC), where slower and higher-level emotional processes occur (Reiman, 1997; van Honk et al., 2005).

Testosterone has been found to reduce subcortical–cortical connectivity. In one functional magnetic resonance imaging (fMRI) study, testosterone administration was found to reduce functional connectivity between the OFC and the amygdala (van Wingen, Mattern, Verkes, Buitelaar, & Fernández, 2010). Intriguingly, individuals with IED do not show the same increases in cortical–subcortical coupling that are observed in control participants when viewing angry faces (Coccaro, McCloskey, Fitzgerald, & Phan, 2007), suggesting that dysfunctional communication between these levels predicts excessive reactive aggression (van Honk et al., 2010). The importance of cortico–subcortical
cross-talk in anger and aggression is supported by recent diffusion tensor imaging (DTI) findings demonstrating that lower white-matter serial–frontal cortical connectivity is associated with more aggressive behavior and impulsivity in healthy volunteers (Peper, de Reus, van den Heuvel, & Schutter, 2015; Peper et al., 2013). This association was mediated by endogenous testosterone levels, providing a possible neural mechanism for the relation between testosterone and approach-related behavior (van Honk et al., 2010).

Communication between subcortical and cortical regions can also be observed in the electroencephalogram (EEG; Schutter, Leitner, Keremans, & van Honk, 2006), with coupling between slow frequencies (delta, 1–4Hz) localized—in part—to regions of the subcortex; and faster frequencies (beta, 12.5–30Hz) localized to the PFC (Velikova et al., 2010). Consistent with fMRI data, coupling between delta and beta frequencies has been shown to decrease with the administration of testosterone (Schutter & van Honk, 2004; van Honk et al., 2004). In contrast, cortisol administration is associated with enhanced connectivity (van Peer, Roeelofs, & Spinlhoen, 2008). Endogenous testosterone is similarly correlated with reduced delta-beta coupling (Miskovic & Schmidt, 2009). Research also suggests that delta–beta coupling is correlated with individual differences in dominance attitudes, and is inversely correlated with increased vigilance to angry faces (Hofman, Terburg, van Wielink, & Schutter, 2013).

We argue that cortical–subcortical connectivity is critical for the generation of socially appropriate responses to environmental features that could produce reactive aggression. When the subcortex is decoupled from cortical control regions, individuals are more likely to respond in a largely disinhibited fashion. That is, activation in the subcortex may predispose individuals to respond aggressively when there is a comitant reduction in top–down regulation by cortical structures, with testosterone and cortisol biasing subcortical activity and cortical–subcortical coupling. Importantly, the two hemispheres of the frontal cortex are functionally heterogeneous: the left frontal cortex is associated with approach motivation, while the right frontal cortex is associated with withdrawal motivation (i.e., the motivational direction model; Harmon-Jones, 2003, 2004). As discussed in the following section, this cortical imbalance has implications for the proclivity to engage in social aggression.

Cortical Imbalances

Empirical support for the motivational direction model has been gathered using different techniques in both healthy and clinical populations, showing that the left frontal cortex is associated with processes related to approach motivation, while the right frontal cortex is associated with processes related to avoidance motivation (Amodio, Devine, & Harmon-Jones, 2008; Harmon-Jones, 2003; Harmon-Jones, Gable, & Peterson, 2010; Harmon-Jones, E., Harmon-Jones, C., Serra, & Gable, 2011; Harmon-Jones, Lueck, Fearn, & Harmon-Jones, 2006; Schutter, De Weijer, Meuwese, Morgan, & van Honk, 2008; Smith & Bell, 2010; Verona, Sadeh, & Curtin, 2009). Behavioral provocation studies have found positive correlations between left frontal cortical activation, approach–related motivation, and anger (Harmon-Jones, 2003; Harmon-Jones et al., 2011; Harmon-Jones & Sigelman, 2001). Also, naturally occurring resting state asymmetries in frontal electrical oscillations and cortical excitability have been shown to correlate with individual differences in approach–avoidance-related motivation in healthy young adults (Schutter et al., 2008). Left-sided frontal electric cortical asymmetries have also been found within the psychopathic population and in imprisoned violent offenders, providing a neural correlate that could explain the approach–motivation–related lifestyle of these individuals that includes sensation seeking, risk taking, and aggression (Hecht, 2001; Keune et al., 2012). Recent evidence suggests that resting state asymmetries recorded over the central scalp locations are more closely linked to response inhibition, whereas asymmetries over the anterior regions of the scalp are more closely linked to aggressive behavior (Hofman & Schutter, 2012).

Furthermore, frontal electric cortical asymmetries have been found in young infants and hold predictive value. For instance, stable left-sided electric frontal asymmetries in infants at 10 and 24 months of age predict externalizing behavior as reflected by approach motivation and aggression, whereas right-sided frontal asymmetries predict internalizing behavior as reflected by avoidance motivation and anxiety when children were 30 months of age (Smith & Bell, 2010). Other results have shown that a rightward frontal asymmetry increases the likelihood of developing future depressive symptoms (Nuslock et al., 2011). A leftward frontal cortical asymmetry is, in turn, predictive for the conversion from bipolar II to bipolar I disorder over a 4.7 year follow-up. These latter findings concur with behavioral approach–system hypersensitivity models stating that trait hypersensitivity to approach motivation and reward may predispose to hypomanic and manic states as reflected by frontal cortical asymmetry (Nuslock et al., 2012). Using fMRI, researchers found increases of blood flow in the left, as compared to the right, dorsolateral prefrontal cortex during approach–related goal pursuit, and that this increase was positively correlated to trait approach motivation (Berkman & Lieberman, 2010). Moreover, an [11C]raclopride positron emission tomography (PET) study found that relative left asymmetries in striatal dopaminergic activity were associated with a higher level of approach motivation (Tomer, Goldstein, Wang, Wong, & Volkow, 2008). These data not only indicate that hemispheric asymmetries are present on the subcortical level, but also suggest reciprocal cortico–striatal–thalamo–cortical interactions.

Additional evidence for the frontal lateralization model of motivation and emotion has been provided by studies deploying repetitive transcranial magnetic stimulation (rTMS) to transiently interfere with frontal cortical functioning. In one study, inhibitory rTMS to the right frontal cortex, causing a leftward...
that externalizing (e.g., aggression) and internalizing (e.g., anxiety) problems may coexist for some individuals (Lara, Pinto, Akiskal, K., & Akiskal, H., 2006). These problems are often found to coexist at the trait level of analysis by summing behavioral responses over many discrete states. It is thus possible that in a specific episode or state (that may only occur for a few milliseconds), approach (or avoidance) motivation may dominate the system and suppress avoidance (or approach) motivation. Such a notion would be consistent with the idea that in a given situation, the organism needs to respond with approach or avoidance when confronted with biologically significant stimuli. Alternatively, anger and aggression have been interpreted as ways of coping with anxiety. From this point of view, anger and aggressive behavior can be considered secondary to the primary motivational tendency associated with anxiety which is avoidance. Furthermore, it has been extensively shown that anxiety has a strong subcortical basis (e.g., the amygdala–septo–hippocampal complex) which together with a naturally left-biased frontal asymmetry may nonetheless result in approach-related behavior. In theory, this interpretation could also explain aggression resulting from defensive motivation that is rooted in fear rather than anger. We speculate that during highly aversive situations, the fight–flight system (Gray & McNaughton, 2003) can be shifted toward “fight” rather than “flight,” wherein the subcortical fear circuit activates the naturally left-biased approach system paralleled by callosal inhibition of the avoidance system.

Cortical Imbalances and the Corpus Callosum

Cortical asymmetries may reflect differences in reciprocal interactions between the hemispheres. Anatomical connections between the hemispheres are established through the corpus callosum which is exclusively found in placental mammals. The corpus callosum is the largest white-matter fiber tract in the human brain, comprised of 200–300 million fibers which are coarsely organized in a topographical fashion (Aboitiz & Montiel, 2003). The majority of callosal projections are homotopic in nature, connecting equivalent regions between the two hemispheres. The anterior third of the corpus callosum, termed the genu, links the prefrontal cortical hemispheres and the anterior cinguli. The rostral part of the callosal body (truncus) links the motor areas, whereas the middle part of the central body interconnects the sensorimotor and auditory areas. Finally, the posterior parts of the corpus callosum link the temporoparietal cortices (isthmus), and the most caudal part of the posterior corpus callosum (splenium) connects the occipital hemispheres (Pandya & Seltzer, 1986). The composition of commissural fibers varies across the several parts of the corpus callosum: Poorly myelinated small-caliber (< 2 μm in diameter) slow-conducting fibers connect the temporal, parietal, and frontal cortices; while highly myelinated large-caliber (> 3 μm in diameter) fast-conducting fibers are most dense in connections between the hemispheres of the premotor, sensorimotor,
and occipital regions. It is generally assumed that the slow-conducting fibers support higher-order processes, whereas the fast-conducting fibers are necessary for midline fusion in the sensory domain. The corpus callosum plays a key role in the processing of the input and output signals of each hemisphere that is necessary for effectively coordinating thought and behavior (Nowicka & Tacikowski, 2011). The cerebral hemispheres operate as semi-independent parallel processing systems, and the inhibitory pathways of the corpus callosum are assumed to be essential for interhemispheric signal transfer and communication (van der Knaap & van der Ham, 2011).

Even though the role of the corpus callosum in aggression has been debated for several years, the idea of commissural abnormalities relating to aggression obtained a more firm empirical basis after reports of abnormal functional cortical asymmetries and reduced interhemispheric electrical signal coherence in violent patients diagnosed with antisocial personality disorder (Flor-Henry, Lang, Koles, & Frenzel, 1991). Additional support for the callosal dysfunction theory of aggression was provided by a positron emission tomography (PET) study showing reduced metabolism in the corpus callosum of murderers pleading not guilty by reason of insanity (Raine, Buchsbaum, & Lacase, 1997). Structural white-matter abnormalities in the corpus callosum have also been verified in psychopathic individuals as compared to controls; and a dimensional parametric analysis showed that the callosal aberrations correlated to antisocial behavior and low autonomic activity (Raine et al., 2003). The observed increased callosal volumes and fiber length in this study were explained by possible neurodevelopmental problems associated with reduced axonal pruning of excitatory commissural fibers.

Other evidence in support of callosal involvement in aggression comes from recent studies using transcranial magnetic stimulation (TMS). Transcranial magnetic stimulation technology provides a unique way of measuring effective connectivity between the hemispheres by assessing signal transfer and transcallosal inhibition in vivo (Ferbert et al., 1992). Transcallosal inhibition (TCI) is based on excitatory callosal fibers targeting inhibitory interneurons on the homotopic area of the contralateral hemisphere. When the primary motor cortex is exposed to a strong but short-lasting electromagnetic pulse, the induced electric current in the brain will activate cortical pyramidal neurons causing a contralateral muscle twitch of, for example, the abductor pollicis brevis. The amplitude of this twitch is called the motor evoked potential (MEP). Transcallosal inhibition can be demonstrated by comparing the amplitude of the MEP to a single unilateral test pulse with the MEP amplitude to a unilateral magnetic test pulse which is preceded by a contralateral magnetic conditioning pulse. When the test pulse is given 10 milliseconds (ms) after the conditioning stimulus, a significant reduction in MEP size of the test response is observed (Ferbert et al., 1992). The fact that TCI is greatly reduced in patients with callosal infarctions (Li, Lai, & Chen, 2012) and even absent in acallosal patients (Meyer, Rãricht, & Woiciechowsky, 1998) suggests that the corpus callosum is the main mechanism underlying interhemispheric inhibition.

Using methods that interleave TMS with EEG (Komsi & Kãhkonen, 2006), significantly higher levels of interhemispheric signal propagation from the right to the left side of the brain were recently demonstrated in aggressive psychopathic offenders as compared to healthy individuals (Hoppenbrouwers et al., 2014). Aggressive psychopathic offenders also displayed increased local intra-cortical inhibition of the right, but not the left motor cortex (Hoppenbrouwers et al., 2013). Taken together, these findings may suggest a less responsive right cerebral hemisphere in aggressive psychopathic offenders that results in reduced commissural inhibition of the approach-related motivational system of the left cerebral hemisphere (Hoppenbrouwers et al., 2014). The latter finding concurs with recent results in which a graph theoretical approach to study anatomical connectivity was used to demonstrate abnormalities in interregional connectivity patterns of the right frontal cortex in psychopaths (Yang et al., 2012). The exact mechanism driving these effects remains unclear at this point; however, deficient axonal pruning of commissural excitatory fibers during neural development may at least in part account for the lower levels of transcallosal inhibition.

A comparable commissural asymmetric pattern has been observed in healthy volunteers in which left-to-right mediated transcallosal inhibition is positively correlated to physical and verbal aggression, and relative dominant left-to-right over right-to-left transcallosal inhibition is predictive for selective attentional bias toward angry facial expressions (Hofman & Schutter, 2009). These results can be interpreted as a cerebral asymmetry that is caused by a dominant left-sided approach system actively inhibiting the right-sided avoidance system in the case of more angry aggressive responses; or a dominant right-sided avoidance system which actively down-regulates the left-sided approach system in the case of less angry aggressive responses. Importantly, these findings indicate that the interrelation between the corpus callosum and aggression can be demonstrated in the normal population (Schutter & Harmon-Jones, 2013).

Interestingly, alterations in callosal transmission may also provide a mechanism for explaining the earlier rTMS findings on the processing of angry facial expressions. The inhibitory effects of rTMS locally down-regulate the excitatory transcallosal output to the contralateral hemisphere, causing a transient functional decoupling and release of callosal inhibition that subsequently increases activity in the opposite hemisphere. This view would be in line with the hemispheric rivalry hypothesis of contralateral hyperactivity following unilateral lesions (Kinsbourne, 1976). Alternatively, cross-reduction of cortical excitability following inhibitory rTMS could be explained by axonal activation of excitatory callosal fibers leading to inhibition of the contralateral hemisphere at higher stimulation intensities (Wassermann, Wedegaertner, Ziemann, George, & Chen, 1998). It has also been shown that alcohol intake causes transient reductions of functional commissural connectivity between the frontal hemispheres (Hoppenbrouwers, 2007).
have looked into the role of the anterior commissure in anger and aggression. Particularly, the callosal fibers running from the right hemisphere to the left seem to be most sensitive to the acute effects of moderate alcohol ingestion. This observation concurs with the idea of tilting hemispheric balance to a dominant relative left-sided cortical asymmetry caused by reduced right-sided innervations of inhibitory commissural fibers. The subsequent brain state, indicative of approach-related motivational tendencies and anger, could at least provide a partial biological account for the well-documented association between alcohol and aggression. The proposed relation between abnormal interhemispheric signal transfer and aggression is further underlined by a study that revealed a link between structural abnormalities of the corpus callosum and suicide behavior in the elderly community (Cyprien et al., 2011). In further support of the latter finding, another study found evidence for volumetric reductions of the genu and isthmus regions of the corpus callosum in euthymic patients suffering from bipolar disorder with a history of suicide attempts (Nery-Fernandes et al., 2012). However, structural neuroimaging is not able to extract information on the functional status of the corpus callosum and direction of callosal signal transfer. However, based on the prior discussion, it can be hypothesized that white-matter abnormalities associated with pathological forms of aggression will be more pronounced in fibers running from the right to the left hemisphere, arguably creating a motivational stance of diminished avoidance-related and increased approach-related behavior. Taken together, the empirical evidence from neuroimaging research and from recent non-invasive brain stimulation studies suggests that the corpus callosum plays a significant role in anger and aggressive behavior. However, even though the reviewed findings are in line with the idea that the corpus callosum plays an important role in the formation of cortical asymmetries of mammals (e.g., Lent & Schmidt, 1993), they do not necessarily provide a conclusive explanation of the cause of the interhemispheric imbalance in relation to anger and aggression.

Although the corpus callosum constitutes the main structures responsible for signal exchange between the cerebral hemispheres, the anterior commissure is an additional forebrain bundle that provides a direct pathway for signal transfer between the cerebral hemispheres. The anterior commissure is a myelinated white-matter fiber tract that crosses the midline of the brain anterior to the third ventricle and connects parts of the temporal and orbitofrontal cortices as well as the insular cortices and amygdala (Raybaud, 2010). From a neuroanatomical perspective, the anterior commissure probably plays a substantial role in motivational processes on the level of the cerebral cortex. For example, the anterior commissure can provide a link for the proposed role of the insular cortices in understanding forebrain motivational asymmetries as asymmetric representations of the autonomic nervous system (Craig, 2005). However, except for one diffusion tensor imaging study showing that the anterior commissure may be implicated in aggressive behavior in children with bipolar disorder (Szaena et al., 2012), to our knowledge, no studies are available that have looked into the role of the anterior commissure in anger and aggression. Finally, information exchange between the two cerebral hemispheres can also occur indirectly via subcortical polysynaptic pathways. In this context, the cerebellar tracts may be of particular interest, as increasing evidence suggests that the cerebellum is involved in affective processes (Schutter, 2013). The cerebellum receives input from the cerebral hemispheres via the pontine nuclei of the brainstem, and projects back to the contralateral cerebral cortex via the deep cerebellar nuclei (Middleton & Strick, 2001), laying an anatomical foundation for information exchange between the cerebral hemispheres. In addition, recent findings suggest the existence of a cerebellar asymmetry analogous to the cerebral asymmetry (Wang, Buckner, & Liu, 2012).

**Conclusion**

Neuroimaging, psychophysiological, and clinical population studies provide convergent evidence that social aggression is underpinned by hormonally driven imbalances within and between subcortical and cortical levels of the brain. Neurobiologically, antagonistic actions between the HPG and HPA axes and diametrically opposite behavioral effects of the end products of these axes—testosterone and cortisol—are the foundation of this model. Increased testosterone levels relative to cortisol levels predispose individuals toward approach motivation, in which they automatically and non-consciously respond to potential threats with dominance and aggression. Furthermore, greater testosterone versus cortisol levels reduces subcortical-cortical coupling, reducing the top-down control that may help to inhibit further aggression. The frontal cortex also shows imbalances. Left frontal cortical activity is associated with approach motivation and anger, whereas right frontal cortical activity is associated with avoidance motivation and anxiety (Harmon-Jones, 2003; van Honk et al., 2010). Additional lines of inquiry suggest that directional differences in signal transmission between each hemisphere also figure centrally in social reactive aggression. Recent interhemispheric connectivity studies with TMS add an important aspect to what is currently known about the relations between directional cortical asymmetries, anger, and aggression, and shed new light on unraveling the biological mechanisms driving aggression. Distinct differences pertaining to the direction of callosal signal transfer between the cortical systems implicated in approach- and avoidance-related motivation are proposed to contribute to the expression of anger and aggression.

**References**


callous area in suicidal and non-suicidal patients with bipolar disorder. *Journal of Affective Disorders*, 142(1-3), 150–155. doi: 10.1016/j.jad.2012.05.001


Winkelman, P. (Eds.), Fundamentals in social neuroscience (pp. 197–226): New York: Guilford Press.


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**13 CULTURAL NEUROSCIENCE**

**Bridging Cultural and Biological Sciences**

Joan Y. Chiao and Katherine D. Blizinsky

**Introduction**

*The Cultural Neuroscience Framework*

Cultural neuroscience is an interdisciplinary field that integrates theory and methods from anthropology, cultural psychology, neuroscience, and genetics to understand diversity in human behavior across multiple time scales (Chiao & Ambady, 2007; Chiao, Cheon,Pornpattananangkul, Mrazek, & Blizinsky, 2013; Cheon, Mrazek, Pornpattananangkul, Blizinsky, & Chiao, 2013; see Figure 13.1). The idea of studying human behavior as an interactive by-product of cultural and biological factors is not new; anthropologists have long examined cultural and biological systems as a means of addressing where human diversity comes from and why. However, not much theoretical or empirical attention has been paid previously to how cultural and biological systems shape the human brain (Leade & Downey, 2012). Theory and method in cultural neuroscience are unique in that this branch of neuroscience emphasizes the study of how cultural, environmental, and biological factors can independently and interactively shape neurobiological processes that predict human behavior (see Figure 13.2). Much progress in cultural psychology has occurred in identifying specific cultural values, practices, and beliefs that emerge due to environmental or ecological factors and subsequently shape behavior. Similarly, decades of advances in human neuroscience and genetics have identified neural and genetic systems that foretell human behavioral patterns. Hence, much can be achieved by integrating aspects of these disciplines in order to gain a better understanding of human diversity.