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Endogenous testosterone and cortisol modulate neural responses during induced anger control

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Research with violent offenders and delinquent adolescents suggests that endogenous testosterone concentrations have the strongest positive correlations with violence among men who have low concentrations of cortisol. The present study tested the hypothesis that testosterone and cortisol would similarly interact to determine neural activation in regions supporting self-regulation in response to anger provocation. Nineteen healthy Asian male participants were insulted and asked to control their anger during functional magnetic resonance imaging (fMRI). When cortisol levels were low, testosterone positively correlated with activation in the dorsolateral prefrontal cortex (dlPFC) and thalamus, but not when cortisol levels were high. During induced anger control, functional connectivity was increased between the amygdala and a top-down prefrontal cortical control network. Moreover, the amygdala-PFC connectivity was strongest among those high in testosterone and low in cortisol. This research highlights a possible neural mechanism by which testosterone and cortisol may influence anger control.

Keywords: Prefrontal cortex; Testosterone; Cortisol; Anger control; Anger.

Modern life demands effective anger control for successful interpersonal functioning. From the inconsiderate driver to the upsetting comment from a romantic partner, people sometimes struggle to control angry feelings and the aggressive behavior they motivate. Anger control has been conceptualized as "the tendency to engage in calming and palliative activities that lower arousal and calm the individual" (Deffenbacher, Oetting, Lynch, & Morris, 1996, p. 576). Research implicates hormones, especially the hormones testosterone and cortisol, as risk factors for aggression and violence (Terburg, Morgan, & van Honk, 2009). Today biological and environmental determinants of anger control are of interest to scientists, mental health professionals, law enforcement, industry, and the public, yet there is relatively little empirical knowledge of the underlying neural and hormonal mechanisms.

THE DUAL-HORMONE HYPOTHESIS: TESTOSTERONE AND CORTISOL

Throughout the world, young men commit more direct and extreme acts of physical aggression than women (Archer, 2004). Because endogenous testosterone levels peak in men around age 30, the androgen has been implicated as a risk factor for aggression. Testosterone is a steroid hormone secreted by the hypothalamic-pituitary-gonadal (HPG) axis and has been implicated in aggression and dominance. In animals, including non-human primates, the link between testosterone

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and aggression is robust (Brain & Haug, 1992). Although testosterone in humans (especially in males) is often thought of as a cause of aggression, the link between concentrations of the hormone and aggressive behavior in humans can be inconsistent (for meta-analytic reviews, see Archer, Graham-Kevan, & Davies, 2005; Book & Quinsey, 2005; Book, Starzyk, & Quinsey, 2001; Eisenegger, Haushofer, & Fehr, 2011). Endogenous testosterone and cortisol concentrations measured at the same time of day are relatively stable for several weeks (Liening, Stanton, Saini, & Schultheiss, 2010). Thus, concentrations of endogenous hormones can be conceptualized as traits (Newman & Josephs, 2009; Sellers, Mehl, & Josephs, 2007).

Recent theory and data support the notion that the effect of testosterone on aggression is moderated by concentrations of another hormone: cortisol (Dabbs, Jurkovic, & Frady, 1991; Popma et al., 2007). Cortisol is a glucocorticoid hormone released by the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol is released in response to stress and has been implicated in submissive behavior, feelings of submissiveness, and inhibition (Denson, Spanovic, & Miller, 2009; Goldsmith & Lemery, 2000). Cortisol is thought to attenuate the effects of testosterone on behavior by reducing activity of the HPG axis and blocking androgen receptors in the prefrontal cortex (Burnstein, Maiorino, Dai, & Cameron, 1995; Tilbrook, Turner, & Clark, 2000). Thus, according to this *dual-hormone hypothesis* (Dabbs et al.,1991; Mehta & Josephs, 2010; Popma et al., 2007), the effect of testosterone on aggression in humans is moderated by cortisol such that testosterone is positively associated with aggression only when cortisol concentrations are low.

Two studies support this notion. Dabbs et al. (1991) found that endogenous testosterone positively correlated with severity of violence among male adolescent offenders only when cortisol was low. Popma et al. (2007) reported the same endogenous dual-hormone interaction in correlating testosterone with impulsive aggression in delinquent male adolescents.

Additional research has examined the effects of acute testosterone administration on neural responses to angry facial expressions. These studies reported that exogenous testosterone increased amygdala activity in response to angry faces (Hermans, Ramsey, & van Honk, 2008) and influenced functional coupling of the PFC–amygdala–brainstem circuit in response to angry and fearful faces (Eisenegger et al., 2011; van Wingen et al., 2010). However, to our knowledge, only one neuroimaging study simultaneously examined both testosterone and cortisol in the context of anger. Specifically, Hermans et al. (2008) found that the combination of high concentrations of endogenous testosterone and low concentrations of cortisol positively correlated with increased activation in the amygdala, brainstem, and lateral PFC in response to threatening, angry faces relative to happy faces.

NEURAL CORRELATES OF ANGER CONTROL

Perspectives on aggression, self-regulation, and emotion regulation informed by psychology, psychiatry, and neuroscience emphasize the role of prefrontal cortical control mechanisms in anger and aggression (Blair, 2004; Davidson, Putnam, & Larson, 2000; Denson, 2011; MacDonald, 2008; Mischel et al., 2011; Raine, 2008; Siever, 2008; Wilkowski & Robinson, 2007). Anger and aggression are thought to be influenced by emotional and executive control mechanisms that bias individuals toward or away from aggressive responses (Davidson et al., 2000; Raine, 2008; Siever, 2008). This research program implicates the dorsal anterior cingulate cortex (dACC), dorsal medial prefrontal cortex (dmPFC), orbitofrontal cortex (OFC), and dorsolateral prefrontal cortex (dlPFC). In clinical populations such as violent offenders and psychopaths, neuroimaging studies show deficits in the structure and function in these regions (Raine, 2008; Yang, Glenn, & Raine, 2008). Evidence suggests that the dmPFC plays a self-referential role in emotion processing, whereas the dlPFC plays a broader regulatory role.

The fact that individuals do not always behave aggressively in the face of provocation when they are able to do so (e.g., are physically capable and not experiencing fear) suggests that (1) prefrontal control processes are often initiated when angered, and (2) individuals differ in the efficiency of recruiting prefrontal neural processes when angered. Evidence for the role of prefrontal control comes from a prior functional magnetic resonance imaging (fMRI) study, in which participants were insulted by the experimenter by being unjustly told in an irritated tone of voice that they did not follow instructions on a difficult anagram task (Denson, Pedersen, Ronquillo, & Nandy, 2009). Provocation increased activation in the dmPFC, dlPFC, including the superior frontal gyrus (SFG), dACC, thalamus, and insula. Although this prior study did not specifically examine anger control, activation in these regions may have supported palliative processes. Moreover, trait aggressiveness was correlated with amplified activity in the dACC. The dACC has been conceptualized as a "neural alarm system" that monitors environmental conflict and recruits

prefrontal cortical control (Eisenberger & Lieberman, 2004). This amplified dACC activation suggests that aggressive individuals required greater recruitment of control processes when provoked.

Another fMRI study investigated individual differences in the high- and low-functioning alleles of the monoamine oxidase-A gene (MAOA-H and MAOA-L, respectively) in response to social exclusion (Eisenberger, Way, Taylor, Welch, & Lieberman, 2007). Relative to MAOA-H individuals, MAOA-L individuals are at risk of increased aggression and antisocial behavior (Brunner, Nelen, Breakefield, Ropers, & van Oost, 1993; Eisenberger et al., 2007; Kim-Cohen et al., 2006; Shih, Chen, & Ridd, 1999). In response to social exclusion, MAOA-L individuals showed more activation in the dACC and SFG than MAOA-H individuals (Eisenberger et al., 2007). Thus, Denson, Pedersen et al. (2009) and Eisenberger et al. (2007) converge on the notion that at least within the confines of the scanner, aggressive individuals show increased recruitment of regions implicated in control in response to upsetting social interactions. The increased recruitment of prefrontal control presumably reflects greater effort exerted by prefrontal regions over subcortically mediated anger and aggressive urges.

THE CURRENT STUDY

The present study examined the hypothesis that the interaction of testosterone and cortisol would influence activity in the neural circuitry underlying prefrontal cortical control and subcortical regions implicated in emotion processes. Because cortisol is thought to block the effect of testosterone, we expected endogenous testosterone to predict increased neural activation only at low concentrations of cortisol. Such a result would be consistent with the notion that high-testosterone individuals invoke increased recruitment of control processes—but only when cortisol is low. In a subtle yet realistic manner, participants were asked to control their emotional responses if insulted by one of the research staff who was ostensibly in a foul mood. Dependent measures were blood oxygen level-dependent (BOLD) responses, self-reported anger, and self-reported anger control. We also examined differences in functional connectivity between baseline and induced anger control in the PFC–amygdala–brainstem circuit and the extent to which this connectivity was jointly influenced by testosterone and cortisol. We expected that the strength of PFC–amygdala–brainstem connectivity during induced anger control would be strongest among those high in testosterone and low in cortisol, as such individuals likely have the most difficulty in controlling angry feelings.

METHOD

Participants and design

Nineteen healthy, right-handed, East and Southeast Asian, male undergraduates (M_{age} = 22.58, SD = 4.05) from the University of New South Wales (UNSW) participated in exchange for AUD$50.[1] All participants were recruited via an advertisement on the university's job-listing website. To reduce suspicion, participants were told that they were participating in an experiment on brain regions associated with cognitive tests. During an initial session in our laboratory (conducted in the late afternoon to control for diurnal hormone fluctuations), participants were screened for handedness and safety. Exclusion criteria included those with endocrine or immune disorders, smokers, and illicit drug users. Participants also provided saliva samples for cortisol and testosterone assessments. All procedures were approved by the Human Research Ethics Committee at UNSW.

Materials and procedure

Baseline mood and hormone assessment

Approximately 3–4 weeks after the initial session, participants arrived at the neuroimaging facility and were greeted by a female undergraduate research assistant and the first author. All imaging occurred between 4 pm and 9 pm. Participants completed the entire state version of the Positive and Negative Affect Schedule–X (PANAS-X; Watson & Clark, 1994) as a measure of baseline mood. Participants were instructed to "indicate to what extent you feel this way *right now*." Of particular interest was the hostility subscale, which assesses angry affect (α = .64). Prior to entering the scanner, participants provided a second saliva sample for cortisol and testosterone.

[1]The recruitment of an Asian sample was unintentional. By chance, all participants who responded to the advertisement and passed safety screening were of Asian background. There is a large Asian student population at UNSW.

Anger control induction

Participants were told that they would be completing neuropsychological tests while in the scanner (an anagram task). In fact, the anagram task was not a neuropsychological test at all, but instead served as the basis for the anger control induction and subsequent provocation. To induce motivation to control angry feelings, upon completion of the pre-scan mood measure, the female experimenter privately told the participants:

> Look, Dr. Denson is in a bit of a grumpy mood today. He's been getting upset at participants during the anagram task for not speaking loud and fast enough. I don't know if it's a problem with the microphone or what, but it's really important that you keep your cool during the study or the data will be worthless. Emotion really interferes with where the brain gets activated, and therefore disrupts our measurement of the cognitive tasks. And this is part of my thesis and we don't have funding for a lot of participants, so you would really be helping me out.

Participants were then escorted to the scanner where a 3D structural scan was acquired, followed by the anagram task and provocation.[2]

Provocation procedure

We used a provocation procedure that has effectively induced anger in prior fMRI research (Denson, Pedersen et al., 2009) and which was adapted from a laboratory provocation manipulation that successfully induces anger and aggression (e.g., Pedersen, Gonzales, & Miller, 2000). Two minutes of functional baseline data were collected while participants were instructed to stare at a green circle in the center of an otherwise white screen visible through mirrors. Participants were then presented with four easy and eight difficult anagrams for 15 s each. They were asked to state their answer out loud or say "no answer" if they did not know the answer. As part of the provocation manipulation, Denson interrupted participants once every 60 s requesting that they speak louder. During the third interruption, which served as the provocation, Denson stated in a rude, upset, and condescending tone of voice "Look, this is the third time I have had to say this! Can't you follow directions?" Immediately following the insult, an additional 2 min of functional data was collected while participants viewed a green circle. Because the insinuation was that participants were not intelligent enough to follow simple instructions, the provocation manipulation represented the delivery of an unjustified insult.

Self-reported anger and anger control

Participants completed a second PANAS-X in relation to how they felt as a result of the provocation (hostility subscale $\alpha = .73$). Specifically, they were instructed to "indicate to what extent you felt during or immediately after the anagram task." Participants also completed five items assessing anger control (e.g., "I tried hard to control my emotions during the scanning"; 1 = not at all, 5 = extremely; $\alpha = .82$; see Appendix). Mean scores were computed for all self-report measures. Finally, the experimenter probed for suspicion, thanked, debriefed, and compensated participants. No participants reported being suspicious of the provocation or true purpose of the study. The first author personally debriefed all participants and ensured that they left in a neutral or positive mood. No participants reported emotional distress after being debriefed.

Hormone assays

Samples were stored in a −20 °C freezer until study completion. They were then assayed by a professional reference laboratory at the University of Dresden, Germany, for cortisol and free testosterone. Sampling tubes were centrifuged for 5 min, and hormone concentrations were measured by commercially available chemiluminescence-immuno-assays with high sensitivity (IBL International, Hamburg, Germany). Intra- and interassay coefficients of variations were below 10%. Because testosterone concentrations measured during the initial session and pre-scan testosterone concentrations were significantly correlated, they were averaged into a reliable baseline composite, $r(18) = .55$, $p = .02$, $M = 75.69$ pg/ml, $SD = 25.06$. Cortisol assessments were only marginally significantly correlated, $r(18) = .43$, $p = .07$, $M_{\text{untransformed}} = 9.04$ nmol/l, $SD = 5.15$; $M_{\text{log-transformed}} = 2.07$, $SD = 0.50$, possibly because cortisol is sensitive to novelty, social evaluation, and psychosocial stress (Denson, Spanovic et al., 2009; Dickerson & Kemeny, 2004). As such, meeting the research staff for the second time should have been less novel and less stressful than the initial session. Therefore, we chose to retain the pre-scan cortisol measure as a less biased cortisol assessment. Tukey's (1977) box-plot procedure identified one outlier for cortisol. As such, we log-transformed cortisol values. As a sensitivity test,

[2] As part of an unrelated study, participants also completed a Stroop and reversal learning task prior to the anagram task.

we also winsorized the single outlier and reanalyzed the data. Winsorizing produced an identical pattern of results as log-transforming.

Image acquisition

Participants viewed the tasks through mirrors, which were presented on a high-resolution monitor placed at the end of a Philips Achieva X-Series 3-Tesla whole-body scanner with an eight-channel head coil and parallel imaging system. Padded foam head constraints controlled movement. Once participants were situated in the scanner, a localizer scan was conducted to ensure proper image acquisition. Next, we acquired a T1 anatomical 3D structural data set (180 slices, FOV = 256 mm, voxel size = 1 × 1 × 1 mm). For functional imaging, a whole-brain EPI pulse sequence with sagittal slices and 2.5 SENSE acceleration was employed (50 slices, slice thickness = 3 mm, voxel size = 2.14 × 2.14 × 3 mm, FOV = 240 mm, TE = 60 ms, TR = 3000 ms, 90° flip angle). The first four volumes were discarded by the scanner.

Statistical analyses

The sagittal EPI slices imaged substantial amounts of non-brain tissue that could interfere with motion correction. Accordingly, as a first step, BET from the FSL package (Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB), University of Oxford, Oxford, UK) (Smith et al., 2004) was used to remove all non-brain components in the EPI images. After this step, the data were imported to BrainVoyager QX (Brain Innovations B.V., The Netherlands. http://www.brainvoyager.com/), with which all subsequent preprocessing was performed. Images were 3D motion corrected and spatially smoothed with a 4.28 mm Gaussian filter. Brains were normalized via Talairach transformation (Talairach & Tournoux, 1988), and regions of interest were checked against the Talairach Daemon (Lancaster, Summerln, Rainey, Freitas, & Fox, 1997). Functional images were coregistered with the normalized structural images. All BOLD responses were adjusted for the hemodynamic response function. We conducted whole-brain, fixed-effects group analyses and controlled type I error with the false discovery rate: $q(\text{FDR}) < .05$, voxelwise $p < .005$.

The provocation was modeled as the difference in activation during the two fixation blocks (i.e., 2 min post-provocation > 2 min baseline fixation contrast). Although the present study's block design did not make use of multiple events, single epoch designs have been used successfully in prior research (e.g., Buchel, Bornhovd, Quante, Glauche, Bromm, & Weiller, 2002; Koyama, McHaffie, Laurienti, & Coghill, 2003); may be preferable where variability arising from sensitization, habituation, and predictability are a concern (Koyama et al., 2003); and they provide increased power for functional connectivity analyses. With respect to the length of the epochs, sustained block designs are frequently used when investigating persistent processes, such as the neural bases of affect (e.g., Kross, Davidson, Weber, & Ochsner, 2009), arousal (e.g., Bühler, Vollstädt-Klein, Klemen, & Smolka, 2008), and sensation (Koyama et al., 2003). In such designs, blocks typically range in length from 30 s (e.g., Kross et al., 2009) to 110 s (e.g., Visscher et al., 2003).

For correlating the BOLD responses with self-report data, hormone concentrations, and other BOLD responses, we selected clusters for these analyses based on the results of our whole-brain analyses. The activity in these clusters was averaged such that mean signal intensity was calculated for each participant for each cluster listed in the tables. The mean activations in each cluster for each participant were based on 40 time points (2 min) at baseline and 40 time points following the provocation. Only these mean values for the significant clusters were exported to SPSS (IBM Corporation, New York, US). We then computed correlations between signal intensity from these averaged clusters and hormone concentrations, self-reported anger control, and anger. To test for cortisol × testosterone interactions, the hormones were mean-centered, and interaction terms were computed with these centered variables (Aiken & West, 1991). For post-hoc probing of interactions, high and low levels of cortisol and testosterone were operationalized as ±1 *SD* from the sample mean following procedures outlined by Aiken and West (1991). All statistical tests are were two-tailed.

To test for functional connectivity, we conducted random-effects Granger causality mapping (GCM) (Roebroeck, Formisano, & Goebel, 2005).[3] Prior to conducting the GCM analyses, functional images were slice scan time corrected (Roebroeck et al., 2005). Individual volume maps were summed and thresholded at $q(\text{FDR}) < .05$ and smoothed with a 2-mm Gaussian kernel. The first and last volumes were deleted in each condition, leaving 38 data points each for the baseline and anger control periods. Because research has implicated the amygdala as a mediating

[3] Although some researchers suggest that GCM should not be used to determine effective connectivity, GCM is an acceptable method for identifying functional connectivity between neural regions across time (as is psychophysiological interaction analysis) (David et al., 2008; Friston, 2009).

region in a neural circuit between prefrontal cortical control and subcortical structures (e.g., the brainstem) in the anger context (Carré, McCormick, & Hariri, 2011; van Honk, Terburg, & Bos, 2011; van Wingen et al., 2010), we used the amygdala as our seed region. To determine whether functional connectivity was jointly moderated by testosterone and cortisol, we standardized the hormone values and computed the testosterone:cortisol ratio (Terburg et al., 2009). We then calculated an image-based correlation map showing correlations between individual differences in the testosterone:cortisol ratio and the strength of functional connectivity estimates from the GCM analyses. Although the initial analyses involving the testosterone:cortisol ratio revealed no significant clusters with $q(\text{FDR}) < .05$, we relaxed our statistical threshold ($p < .05$ uncorrected, minimum 10 voxel extent) and limited our inspection only to overlapping regions identified in the previous GCM analyses.

RESULTS

Self-reported anger and anger control

Participants reported an increase in anger from baseline as a result of the provocation ($M_{\text{pre}} = 1.54$, $SD_{\text{pre}} = 0.56$ vs. $M_{\text{post}} = 1.96$, $SD_{\text{post}} = 0.76$), $t(18) = 2.46$, $p = .02$, $d = .57$. Moreover, participants reported controlling their emotions during the study at a level significantly different from the scale endpoint (1 = not at all; $M = 2.97$, $SD = 0.92$), $t(18) = 9.13$, $p < .001$. This self-report is corroborated by the fact that the effect size of the anger increase in the present research was approximately one-third of the effect size in prior research using the same provocation ($d = 1.52$ in Denson, Pedersen et al., 2009). Angry affect was correlated with anger control, such that higher levels of anger experience were associated with higher self-reported effort toward anger control, $r(18) = .46$, $p = .047$. The only significant changes in the remaining PANAS scales were an increase in surprise from baseline, $t(18) = 2.41$, $p = .027$, and a trend toward decreased basic positive affect, $t(18) = -1.74$, $p = .099$. These findings support the specificity of the anger induction. Taken together, these data suggest an effective and specific provocation procedure and anger control induction.

BOLD responses to the anger control induction

The whole-brain post-provocation versus baseline contrast revealed significant activation in the left dACC, right anterior insula, dlPFC (i.e., SFG), thalamus, and an area extending across the left dmPFC and dACC (see Table 1). The dlPFC activation was bilateral, but more widespread in the left hemisphere than the right. Because of the large left dlPFC activation, for the regression and correlational analyses, signal intensity from three large portions of the cluster were extracted in order to specify more precisely the neural correlates of the phenomena under study. Although amygdala and brainstem activation were not detected in the whole-brain analyses, we conducted targeted anatomical region-of-interest (ROI) analyses on the bilateral amygdala and brainstem. Anatomical ROIs were based on a T1 anatomical scan, and coordinates were checked against the Talairach Daemon atlas. For the amygdala, we defined our ROI as a 10-mm cube centered at Talairach coordinates $x = \pm 23$, $y = -4$, $z = -17$, and used a more liberal statistical threshold, $p < .02$ uncorrected, 10 voxel extent. We also specified an anatomical ROI for the brainstem ($x = \pm 25$, $y = -12$ to -39, $z = -1$ to -38). These

TABLE 1
Prefrontal and subcortical brain regions active in response to induced anger control (provocation > baseline contrast)

			Talairach coordinates				*Significance test*	
Region of activation	*Hemisphere*	*Brodmann area*	*x*	*y*	*z*	*Cluster size (Voxels)*	*t statistic*	*p value*
dACC	Left	32	−2	14	34	685	3.63	.000289
dmPFC/dACC	Left	6/24	−4	4	47	429	4.23	.000025
SFG_{LEFT1}	Left	9	−7	58	31	708	5.21	<.000001
SFG_{LEFT2}	Left	9	−22	58	26	564	4.60	.000005
SFG_{LEFT3}	Left	10	−35	55	14	341	4.40	.000011
SFG_{RIGHT}	Right	9	15	58	32	564	4.41	.000011
Insula	Right	13	40	11	−4	594	4.52	.000007
Thalamus	Right		11	−25	10	244	3.91	.000096
Thalamus	Left		−19	−24	15	289	4.38	.000013
Amygdala	Left		−28	−5	−17	11	2.17	.030399
Brainstem	Bilateral		0	−14	−20	299	4.10	.000043

TABLE 2
Zero-order correlations between testosterone, cortisol, and BOLD signal following provocation

Region of activation	*Testosterone*			*Cortisol*		
	r	*95% CI*	*p*	*r*	*95% CI*	*p*
dACC	.21	(−.27, .61)	.38	.24	(−.24, .63)	.33
dmPFC/dACC	.18	(−.30, .59)	.46	.06	(−.41, .50)	.82
SFG_{LEFT1}	.56	(.14, .81)	<.01	.19	(−.29, .59)	.44
SFG_{LEFT2}	.46	(.01, .76)	<.05	.18	(−.30, .59)	.46
SFG_{LEFT3}	−.06	(−.50, .41)	.81	.31	(−.17, .67)	.20
SFG_{RIGHT}	.35	(−.12, .69)	.14	.28	(−.20, .65)	.24
Insula	.65	(.28, .85)	<.01	.44	(−.02, .75)	.06
$Thalamus_{RIGHT}$	.13	(−.34, .55)	.61	.45	(−.01, .75)	.05
$Thalamus_{LEFT}$	−.19	(−.59, .29)	.44	.05	(−.41, .49)	.84
Amygdala	−.07	(−.51, .40)	.78	.05	(−.41, .49)	.85
Brainstem	.07	(−.40, .51)	.78	−.03	(−.48, .43)	.90

Note: p values are two-tailed.

analyses revealed a small area of activation in the left amygdala and a larger area in the brainstem (Table 1). The whole-brain provocation versus baseline contrast revealed additional activations in the cerebellum, caudate, and occipital lobe; however, as these regions were not relevant to the current study's hypotheses, we did not examine these further. The reverse contrast (post-provocation versus baseline) revealed increased activation only in white matter in the posterior cingulate ($x = -10$, $y = -7$, $z = 27$; 64 voxels, $t = 3.25$, $p = .001$).

Main effects of testosterone and cortisol

Testosterone was positively correlated with BOLD responses in the right dlPFC and insula (ps $< .05$; see Table 2). Cortisol was positively correlated with BOLD responses in the right thalamus ($p = .05$) and a trend toward significance in the insula ($p = .06$).

Testosterone × cortisol interactions

Regression analyses revealed a significant testosterone × cortisol interaction for activity in the left SFG ($x = -22$, $y = 58$, $z = 26$), $b = -0.054$, $t(15) = -2.793$, $p = .014$, $R^2_{adjusted} = .38$. Follow-up analyses revealed that there was a significant relationship between testosterone and BOLD responses at low levels of cortisol, $b = 0.06$, $t(15) = 4.60$, $p < .001$, but not at high levels of cortisol, $b = 0.002$, $t(15) = 0.32$, $p = .75$. Although the testosterone × cortisol interaction for the right SFG ($x = 15$, $y = 58$, $z = 32$) did not reach conventional levels of statistical significance, $b = -0.049$, $t(15) = -1.63$, $p = .12$, $R^2_{adjusted} = .15$, we conducted post-hoc probing on an exploratory basis. These results paralleled the previous interaction such that there was a significant relationship between testosterone and BOLD responses at low levels of cortisol, $b = 0.05$, $t(15) = 2.12$, $p = .049$, but not at high levels of cortisol, $b = 0.003$, $t(15) = 0.15$, $p = .89$ (see Figure 1). There was also a significant testosterone × cortisol interaction for activity in the right thalamus (x = 11, y = −25, z = 10), $b = -0.05$, $t(15) = -2.61$, $p = .02$, $R^2_{adjusted} = .34$. Post-hoc probing revealed a significant relationship between testosterone and BOLD responses in the thalamus at low levels of cortisol, $b = 0.04$, $t(15) = 2.19$, $p = .045$, but not at high levels of cortisol, $b = -0.02$, $t(15) = -1.38$, $p = .19$ (see Figure 2).

Functional connectivity analyses

The separate GCM results for the baseline period and anger-control period are presented in Figure 3. Using the significant cluster in the left amygdala as the seed region, the GCM analyses showed that, during baseline, functional connectivity was greatest between the right OFC, SFG, brainstem, and amygdala time courses. That is, earlier BOLD values from the OFC, SFG, and brainstem time courses predicted subsequent BOLD responses in the amygdala. During baseline, there was no functional connectivity between the amygdala and left PFC. However, these patterns of connectivity were reversed following provocation: there was an increase in functional connectivity between the amygdala and a top-down prefrontal cortical control network consisting of the left dlPFC, left dACC, and left OFC. That is, earlier BOLD values in the amygdala time course predicted subsequent BOLD responses in the prefrontal cortical control network. The brainstem–amygdala connectivity was no longer observed during the anger-control period.

Inspection of the regions identified in the GCM analyses revealed that the testosterone:cortisol ratio was positively correlated with connectivity strength between the right ventromedial prefrontal cortex (vmPFC) and left amygdala during baseline (Figure 4). Moreover, the testosterone:cortisol ratio was positively correlated with connectivity strength between the left amygdala and the left dACC and dlPFC during the anger-control period.

Neural correlates of subjective experience

Because self-reported anger and anger control were correlated, we computed partial correlations between each self-report variable and brain activation while

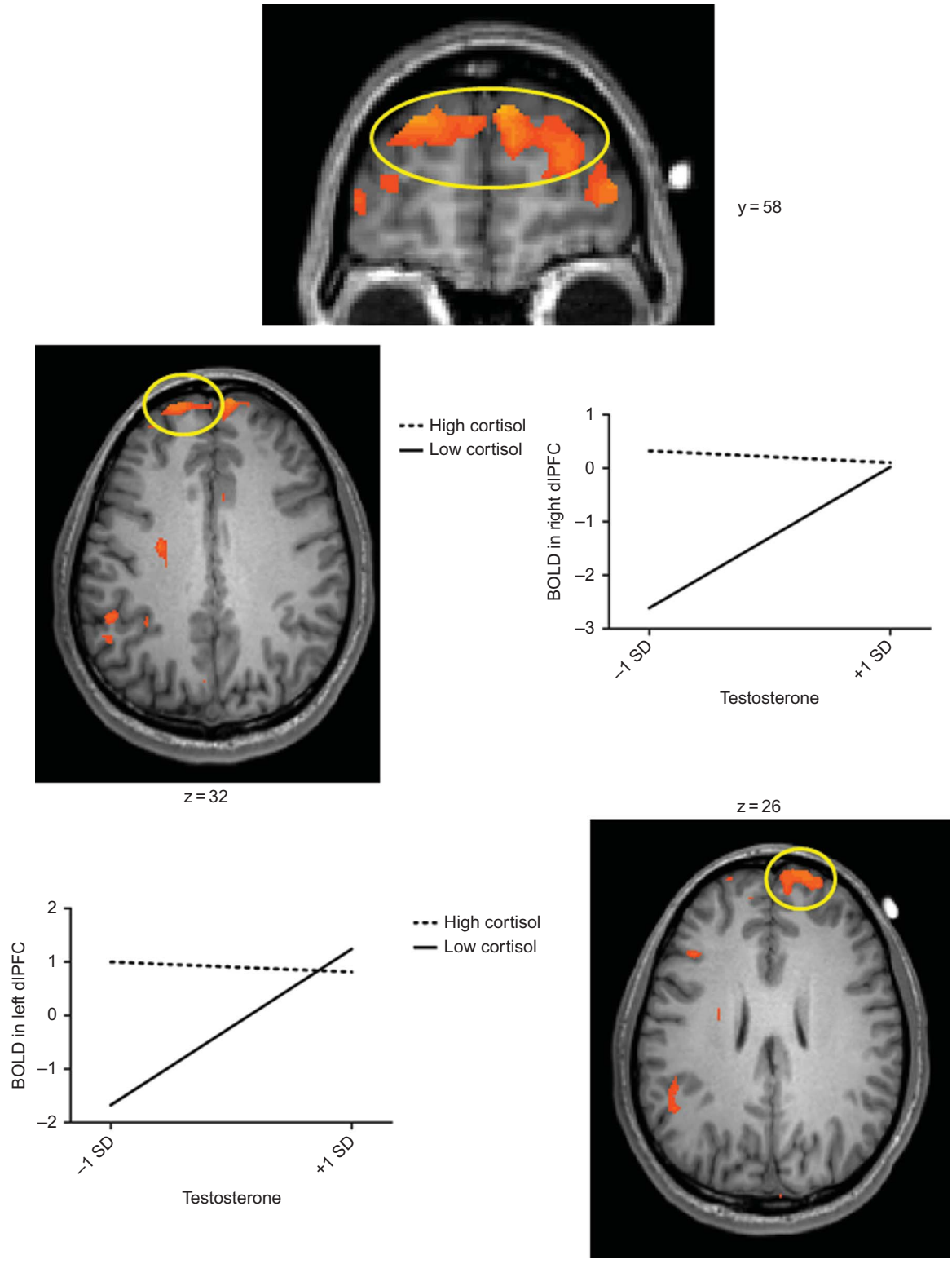

Figure 1. Endogenous testosterone and cortisol interact to influence activation in the dlPFC during induced anger control. Participants were asked to control their anger in response to an unjustified insult. The regression analyses examined the clusters circled in yellow. Bilaterally, endogenous testosterone was positively correlated with dlPFC activation only at low levels of endogenous cortisol ($ps < .05$). Parameter estimates for BOLD responses are standardized.

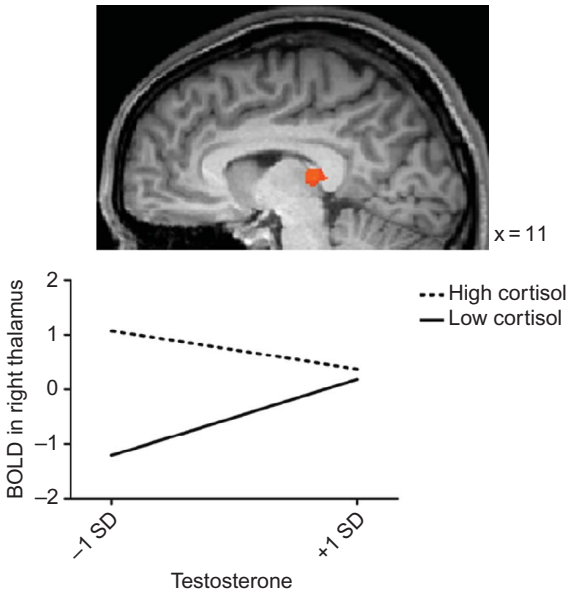

Figure 2. Endogenous testosterone and cortisol interact to influence activation in the right thalamus during induced anger control. Endogenous testosterone was positively correlated with thalamus activation only at low levels of endogenous cortisol (*p*s < .05). Parameter estimates for BOLD responses are standardized.

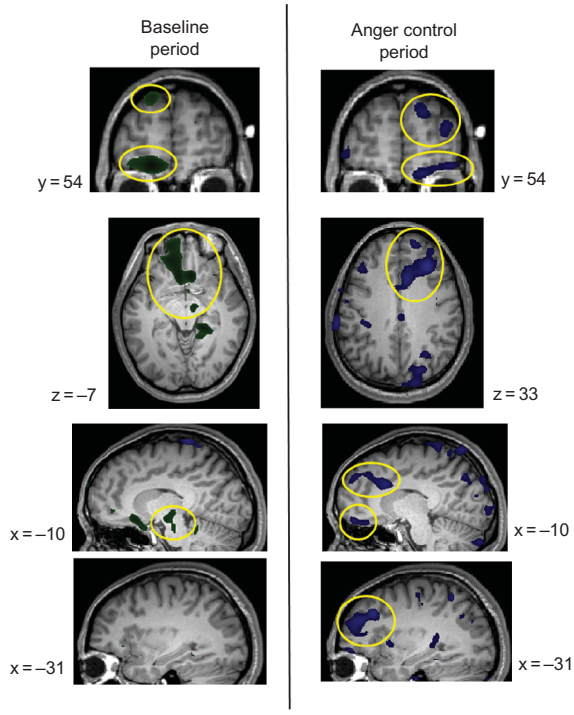

Figure 3. Functional connectivity analyses. The significant cluster in the left amygdala was specified as the seed region (see Table 1). The images on the left show the results during baseline, and the right images show the results for the anger-control period. As indicated by the green voxels, during the baseline period, activation across the period in the right dlPFC (top panel), right OFC (top two panels), and brainstem (second and third panels) was correlated with the subsequent amygdala time course. During baseline, there was no functional connectivity between the amygdala and left PFC (bottom panel). However, during induced anger control, the amygdala time course predicted recruitment of a top-down prefrontal cortical control network consisting of the left dlPFC (first two panels and bottom panel), left dACC (second and third panels), and left OFC (first and third panels). The brainstem–amygdala connectivity was no longer observed during the anger-control period (third panel).

controlling for the other. These analyses showed that the dmFPC/dACC and right anterior insula were significantly correlated with increased self-reported anger control and marginally with decreased anger (see Table 3).

DISCUSSION

The present research provides insight into how endogenous hormone concentrations may influence neural mechanisms underlying anger control. Specifically, when participants were asked to control their emotional response to provocation, testosterone was correlated with amplified BOLD responses in the dlPFC and thalamus when levels of cortisol were low but not when cortisol levels were high. These hormonal effects on neural activity parallel prior work on the behavioral effects of testosterone and cortisol on aggression and dominance (Dabbs et al., 1991; Mehta & Josephs, 2010; Popma et al., 2007). This is noteworthy as the dlPFC is an important region broadly involved in self-regulatory control including emotion regulation (Heatherton & Wagner, 2011; Ochnser & Gross, 2008), and the thalamus has been implicated in anger, emotional processing, emotion experience, representing feelings, and emotional control (Hooker, Verosky, Germine, Knight, & D'Esposito, 2008; Marchand, 2010; Phan, Wager, Taylor, & Liberzon, 2002; Reiman et al., 1997).

Functional connectivity analyses examining the PFC–amygdala–brainstem circuit revealed that during baseline, the vmPFC, OFC, and dlPFC time courses predicted subsequent BOLD responses in the amygdala. Moreover, the strength of connectivity was partially influenced by concentrations of testosterone relative to cortisol. Those with high concentrations of testosterone relative to cortisol showed increased connectivity between the vmPFC and amygdala. This result is consistent with an fMRI study that reported increased amygdala–vmPFC coupling in MAOA-L individuals when viewing angry and fearful faces relative to non-emotional stimuli (Buckholtz et al., 2008). Increased amygdala–PFC connectivity has also

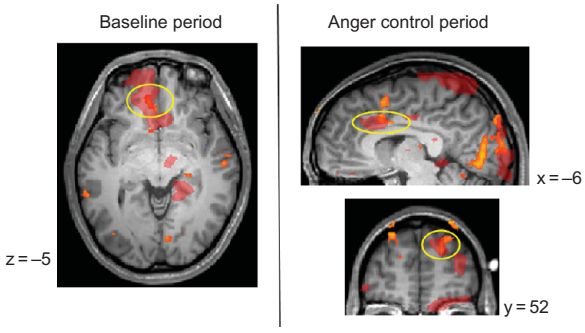

Figure 4. Correlations between participants' testosterone: cortisol ratios and strength of connectivity during baseline (left panel) and during the anger-control period (right panel). The translucent red areas are the regions of connectivity identified in the functional connectivity analyses (see Figure 3). Activated voxels show positive relationships between the testosterone:cortisol ratio and strength of connectivity. Thus, individuals with high testosterone:cortisol ratios showed stronger connectivity of the left vmPFC with the left amygdala during baseline (left panel), and also stronger connectivity of the left amygdala with the right dACC (top right panel) and right dlPFC (bottom right panel) during induced anger control.

TABLE 3
Partial correlations between self-reported anger control and state anger with neural activation following provocation

Region of activation	*Anger control*			*State anger*		
	r	*95% CI*	*p*	*r*	*95% CI*	*p*
dACC	.34	(−.14, .68)	.17	−.13	(−.55, .34)	.61
dmPFC/dACC	.48	(.03, .76)	.05	−.44	(−.75, .02)	.07
SFG_{LEFT1}	.04	(−.42, .48)	.88	.23	(−.25, .62)	.35
SFG_{LEFT2}	.40	(−.07, .72)	.10	−.34	(−.69, .14)	.17
SFG_{LEFT3}	.28	(−.20, .65)	.27	−.34	(−.69, .14)	.17
SFG_{RIGHT}	.23	(−.25, 62)	.36	−.19	(−.59, .29)	.45
Insula	.57	(.15, .81)	.01	−.42	(−.73, .04)	.08
$Thalamus_{RIGHT}$	.19	(−.29, .59)	.45	−.21	(−.61, .27)	.40
$Thalamus_{LEFT}$	−.16	(−.57, .32)	.52	−.28	(−.65, .20)	.25
Amygdala	−.18	(−.58, .30)	.48	.02	(−.44, .47)	.94
Brainstem	.05	(−.41, .49)	.84	.18	(−.30, .59)	.47

Note: p values are two-tailed.

been implicated in fear reduction following threat (Klumpers et al., 2010).

However, the baseline connectivity results diverge somewhat from a recent theoretical proposition on the effect of testosterone on brain activation during situations involving status threat (van Honk et al., 2011; see also Carré et al., 2011). One implication of van Honk et al. (2011) is that the state of low-status threat induced during our baseline period should cause the brain to run in "safeguarding mode" among those high in testosterone. Safeguarding involves a decoupling of the OFC with the amygdala, resulting in impaired inhibitory control of the OFC over the amygdala. However, in the present case, we did not observe hormonal modulation of the OFC–amygdala connectivity. Rather, we observed increased vmPFC–amygdala connectivity at baseline among those high in testosterone and low in cortisol, and this presumably occurred because participants were attentive to emotional threats in light of the forewarning regarding possible provocation from the experimenter. In other words, this may represent effort at preemptive cortical control over the amygdala prior to an expected status threat. Nonetheless, it is worth noting that the theory papers of van Honk et al. (2011) and Carré et al. (2011) do not consider how testosterone may interact with other hormones to determine neural responses. Our results emphasize the importance of considering interactions with cortisol as well.

Following the provocation, the pattern of connectivity shifted to the left hemisphere along with early amygdala BOLD responses predicting subsequent responses in the dlPFC and dACC, suggesting that these regions responded to impulses generated or mediated by the amygdala. Indeed, increases in prefrontal left hemisphere activation typically occur when individuals are angered (Carver & Harmon-Jones, 2009; Harmon-Jones & Sigelman, 2001). Moreover, those high in testosterone relative to cortisol showed increased functional connectivity between the amygdala and PFC (i.e., dACC and dlPFC) during anger control.

The connectivity data suggest two complementary explanations. First, when engaging in anger control, such individuals required greater recruitment of the PFC in response to amygdala activation than participants with low levels of testosterone relative to cortisol. An additional possibility is that those high in testosterone relative to cortisol had more inefficient prefrontal cortical control over the amygdala (possibly to some extent even at rest). The former suggests a strong subcortical response in need of greater control, whereas the latter suggests less efficient control mechanisms. Although these results should be interpreted cautiously due to the small sample size, future research that orthogonally manipulates testosterone and cortisol administration may provide further insights into the role of hormones on anger control.

The present research also sheds light on brain regions associated with the phenomenology of induced anger control. Specifically, the dmPFC/dACC and the right anterior insula were correlated with increased self-reported anger control, consistent with the notion that prefrontal regions supporting control processes are involved in the subjective experience of anger control. The dmPFC is active when individuals reflect on their emotional state (e.g., Lane, Fink, Chua, & Dolan,

1997). In the present study, this increased activation may reflect self-awareness of one's angry mood. The activation of the right anterior insula is not surprising, as cardiovascular arousal is a common consequence of provocation, and part of calming oneself in response to provocation involves lowering cardiovascular arousal (e.g., heart rate). Because the insula is implicated in interoception and self-awareness, as well as negative emotions including anger, activation in this region could have been associated with increased awareness of becoming agitated, which subsequently led to increased efforts at anger control (Craig, 2003; Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004; Damasio, 1994; Denson, Pedersen et al., 2009; Phan et al., 2002). The insula might form part of a feedback loop in which awareness of anger increased efforts at controlling this negative emotion.

The present study was limited in some regards. For instance, our sample consisted only of young men of Asian ethnicities. Future research might examine the extent to which our findings extend to other ethnic groups, older individuals, and women. Another issue concerns a complementary interpretation of our findings. Our theorizing was guided by the dual-hormone hypothesis such that the effect of testosterone on neural activation would only be observed when cortisol concentrations were low, as cortisol is thought to block androgen receptors in the prefrontal cortex (Burnstein et al., 1995; Tilbrook et al., 2000). However, the nature of the interactions observed is equally consistent with the notion that cortisol influenced neural activation only when testosterone levels were low. Moreover, participants in the present study were told before the scan that they were likely to be treated rudely by the experimenter. This priming was used to ensure that participants were sufficiently motivated to regulate their emotional reactions to the provocation, but it may be that participants became anxious prior to the insult during the baseline period. Thus, although the self-reported emotional responses showed effects only for anger and surprise, and not anxiety, future research might include the exhortation to control emotions without forewarning of the upcoming anger provocation.

Concluding remarks

By examining neural activation in a situation in which participants were asked to control anger in response to a provocation, the present study increases our understanding of hormonal risk factors that demand greater control of aggression. Future work can further refine our insight into the interplay between testosterone, cortisol, and activity within the neural circuitry underlying anger, aggression, and their control. Such work could eventually contribute to more individualized anger-control interventions. Indeed, mental health treatments for anger are less effective than treatment for other emotional problems (Norcross & Kobayashi, 1999). A meta-analysis of anger-management programs found much smaller improvement than those reported for anxiety or depression interventions (DiGiuseppe & Tafrate, 2003). Although still a long way off, the present work represents a step toward forming evidence-based anger-regulation interventions that could possibly take individual differences in hormone concentrations and neural activation into account.

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APPENDIX

Using the following scale, please answer each of the following questions.

1	*2*	*3*	*4*	*5*
very slightly or not at all	a little	moderately	quite a bit	extremely

1. _____ I was motivated to control my emotions during the scanning.
2. _____ I tried hard to control my emotions during the scanning.
3. _____ I was successful at controlling my emotions during the scanning.
4. _____ It took a lot of effort to control my emotions during the scanning.
5. _____ I tried to reduce the intensity of my emotions during the scanning.