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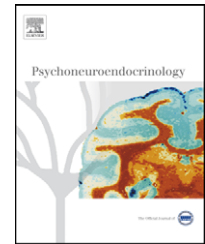


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Amygdala activity to fear and anger in healthy young males is associated with testosterone

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Summary Neuroimaging studies have documented modulation of the activity of the amygdala – a key node in the neural network underlying emotion perception and processing, and one that has also been associated with regulating aggression – by exogenous testosterone. However, results on the impact of normal range testosterone levels on explicit emotion recognition as a prerequisite for social interaction and amygdala activation in healthy young males are missing.

Hence, we performed functional MRI at 3 T in a group of 21 healthy males during explicit emotion recognition with a protocol specifically optimized to reliably detect amygdala activation. We observed similar amygdala activation to all emotions presented without any effect of gender of poser or laterality. Reaction times to fearful male faces were found negatively correlated to testosterone concentration, while no significant effects emerged for other emotions and neutral expressions. Correlation analyses revealed a significant positive association between testosterone levels and amygdala response to fearful and angry facial expressions, but not to other expressions. Hence, our results demonstrate that testosterone levels affect amygdala activation and also behavioral responses particularly to threat-related emotions in healthy young males. We conclude that these findings add to our understanding of emotion processing and its modulation by neuroendocrine factors.

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1. Introduction

Converging evidence has shown that testosterone levels are associated with basic social abilities, e.g., facial mimicry as one component of empathic behavior (Hermans et al., 2006a), mood and selective attention to angry faces (Van

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Honk et al., 1999), and also moderation of the reinforcing qualities of angry faces (Wirth and Schultheiss, 2007). While animal research has unequivocally demonstrated the connection between elevated testosterone levels and increased aggressiveness (e.g., Lumia et al., 1994; Melloni et al., 1997) in human studies only correlational evidence has been reported (e.g., Dabbs et al., 1995; Archer, 2006). Regarding the possible anxiolytic effect of testosterone, this phenomenon has been replicated many times and in a large variety of animal species (e.g., Aikey et al., 2002). Although there is evidence for antidepressant effects in hypogonadal depressive patients after testosterone treatment (e.g., Wang et al., 1996), clear reductions in fear after testosterone administration or treatment have rarely been reported for humans (Van Honk et al., 2005; Hermans et al., 2006b).

The special role of the amygdala in the processing of threat-related stimuli, in particular anger and fear is well documented (e.g., Adolphs, 2002). Consequently, it has been argued to be strongly involved in the pathways controlling aggression, and most neuroimaging studies have consistently observed amygdala activation to angry facial expressions (e.g., Whalen et al., 2001).

Recently, several neuroimaging studies have shown a modulating effect of testosterone on amygdala activation: Van Wingen et al. (2008a) used an emotion matching task and administered a single dose of testosterone to middle-aged healthy females. This modulated amygdala activation, leading to a higher reactivity comparable with the one of young, healthy females. Also, applying exogenous testosterone to healthy young females who were presented with angry faces in a passive viewing task, Hermans et al. (2008) observed stronger amygdala activation in subjects to whom higher testosterone doses had been administered.

Studies investigating possible association of testosterone levels with explicit emotion recognition, another basic prerequisite for social interaction, and the underlying amygdala activation are totally missing. Hence, we investigated whether normally distributed testosterone levels in healthy young males exert an influence on explicit emotion recognition and amygdala reactivity. We performed functional magnetic resonance imaging (fMRI) using an explicit emotion recognition paradigm in healthy young males. Based on previous results from our group (e.g., Habel et al., 2007; Derntl et al., 2008a), we hypothesized amygdala activation to all emotions presented. Moreover, we hypothesized a significant positive association between testosterone levels and amygdala reactivity in healthy males especially to threat-related stimuli as shown by previous fMRI studies in healthy females (Hermans et al., 2008; Van Wingen et al., 2008a) and behavioral data (Van Honk et al., 1999; Wirth and Schultheiss, 2007). In light of assumptions that males respond more strongly to male faces (cf. Mazurski et al., 1996), we also investigated this aspect by presenting both female and male faces.

2. Materials and methods

2.1. Sample

Twenty-one right-handed healthy males aged 21–33 years (mean age 25.1 years, S.D. = 3.5) were enrolled in the study.

Participants were all students (mean education 17.9 years, S.D. = 3.2) and were recruited by advertisements at the University of Vienna and the Medical University of Vienna, Austria. The study was approved by the ethics committee of the Medical University of Vienna and written informed consent was obtained from all subjects prior to the examination.

The presence of psychiatric disorders (according to DSM IV) was excluded on the basis of the German version of the Structured Clinical Interview for DSM (SCID, Wittchen et al., 1997) conducted by experienced clinical psychologists. The usual exclusion criteria for MRI were also applied and all participants had a negative drug screening.

All subjects performed above average according to norms on several neuropsychological tasks taken from the computerized neuropsychological test battery (Gur et al., 1992) engaging nonverbal intelligence, cognitive flexibility, visual learning and memory. No subject was alexithymic, measured with the Toronto Alexithymia Scale 20 (Bagby et al., 1994). All tests were presented with an Apple Macintosh G3 Powerbook using Powerlab software (System General, Milpitas, CA, USA).

Blood samples were taken on the day of fMRI measurements and only males without any hormone treatment were included to prevent any influences of external hormone administration. Assays were analyzed by the Institute for Laboratory Diagnostics of the Medical University of Vienna, Austria, using an electrochemiluminescence-immunoassay (ECLIA, Johnson et al., 1993). The intra-assay accuracy was over 90% (i.e., coefficient of variation was 4–8%) and the sensitivity of each assay was 0.2 ng/ml.

2.2. Functional tasks

We applied the same explicit emotion recognition task as described in detail elsewhere (Derntl et al., 2008a). Briefly, the stimulus material consisted of 72 color photographs of facial expressions portraying an equal number of the five basic emotions (anger, disgust, fear, happiness and sadness) as well as neutral expressions. Subjects were instructed to choose the correct emotion from two verbal possibilities presented on the left and right of the image, by pressing the corresponding button of a response box using the right hand. One of the options was correct and the other was selected at random from all other choices. Emotional facial expressions were presented for a maximum of 5 s with a variable interstimulus interval (ISI) ranging from 12 to 18 s (during which subjects viewed a scrambled face with a central crosshair). Responses triggered immediate progression to the next ISI. Stimuli were projected onto a screen and viewed by the participants via a mirror mounted on the head coil. The presentation of images, recording of responses and acquisition of scanner triggers (one per repetition time) was achieved using the Presentation software package (Neurobehavioral Systems Inc., Albany, CA, USA).

2.3. Behavioral data analysis

The behavioral data acquired during scanning (recognition accuracy and reaction time) were analyzed with repeated measures ANOVAs, with emotion and gender of poser as within-subjects factor. Greenhouse–Geisser corrected

p-values were used for all ANOVAs and post hoc results were Bonferroni corrected.

To further analyze a possible association between testosterone levels and behavioral performance during scanning, correlation analyses between behavioral parameters and hormone level was performed across the whole sample, and results were corrected for multiple correlations.

2.4. fMRI acquisition parameters and data processing

Data acquisition and data processing steps are described in greater detail elsewhere (Derntl et al., 2008a). We used an echo-planar-imaging (EPI) protocol which is optimized for measuring amygdala activation at 3 Tesla (Robinson et al., 2004, 2008) and has been proven to acquire robust signal from the amygdala during emotion processing (Habel et al., 2007; Moser et al., 2007; Derntl et al., 2008a). Imaging was performed with a 3 Tesla Medspec whole-body scanner (Bruker Biospin, Ettlingen, Germany) at the MR Centre of Excellence, Medical University of Vienna, Austria, using gradient-recalled EPI with 10 oblique axial slices centered on the amygdala employing asymmetric *k*-space sampling (FOV = 25 cm × 21 cm, matrix size 128 × 91, slice thickness 2 mm, slice gap 0.5 mm, TR = 1000 ms, TE = 31 ms).

2.4.1. Data preprocessing

Functional data were preprocessed using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/spm2.html>). Images were slice timing corrected, realigned to the mean image and normalized into the standardized stereotactic space and functional data sets were spatially smoothed using an isotropic Gaussian kernel with a full-width-at-half-maximum of 9 mm.

For this event-related design, each stimulus was modelled with a separate regressor, based on the individual response period convolved with the canonical hemodynamic response function and its temporal derivative. Regressors of each valence were pooled to assess brain responses to each emotion leaving a minimum of 12 stimuli per category for statistical analysis. Statistical analysis was performed at the individual and group level. For the group analysis, contrast images from all subjects were included in a second level random effects analysis. Activation differences in brain regions covered with our protocol were examined by applying a two-way ANOVA with emotion and gender of poser as within-subject factors. For the whole slab analysis and direct comparisons results are presented at a threshold of $p < .001$ (uncorrected).

2.4.2. ROI analysis

Since our main hypothesis focused on the amygdala we performed a ROI analysis with the aim of maximizing the sensitivity to changes in amygdala activity and to assess possible hemispheric lateralization effects. Values for amygdala ROIs were extracted using a template based on the MNI single subject brain (Tzourio-Mazoyer et al., 2002), as defined in MRICro (<http://www.sph.sc.edu/comd/roden/template.html>). Mean parameter estimates were extracted for left and right amygdala ROI in each condition (threshold of $p < .001$ uncorrected) and Levene tests for homogeneity of variances indicated homoscedasticity for

all parameter estimates of all emotions as well as left and right amygdala.

A three-way ANOVA was applied with emotion, gender of poser and laterality as repeated factors. Greenhouse–Geisser corrected *p*-values are presented.

2.4.3. Corollary analyses

Correlation analysis was performed for each emotion between testosterone level and mean parameter estimates within the amygdala, provided by ROI analyses, applying Pearson correlations across all participants. Results were corrected for multiple correlations.

3. Results

Mean testosterone level across the whole group was 5.69 ng/ml (S.D. = 1.6), and testosterone levels of all male subjects were within the normal range for 17–50 year old healthy males (2.8–8.0 ng/ml), except for one showing 1.96 ng/ml and another subject whose testosterone level was 8.17 ng/ml.

3.1. Behavioral data

For the emotion recognition performance the repeated measures ANOVA revealed a significant emotion effect ($F(3.306, 66.112) = 3.565, p = .016$), with highest accuracy for happy expressions, no significant gender of poser effect ($F(1, 20) = .186, p = .671$) but a significant emotion-by-gender of poser interaction ($F(5, 95) = 16.132, p < .001$) was apparent. Post hoc tests decomposing this significant interaction revealed that male expressions of fear were significantly better recognized compared with the corresponding female expressions ($p < .001$), but for disgust ($p < .001$) female expressions were recognized more accurately than the male ones. For all other emotions no significant difference remained after Bonferroni correction (all $p > .021$).

Similarly, reaction times exhibited a significant emotion effect ($F(5, 100) = 14.012, p < .001$) with fastest reaction times for happy expressions. However, neither a significant gender of poser effect ($F(1, 20) = .002, p = .964$) nor emotion-by-gender of poser interaction ($F(5, 100) = 1.912, p = .124$) was observed. Fig. 1 illustrates recognition accuracy and reaction times across emotions and neutral expressions.

Correlation analyses after correction for multiple correlations between hormonal levels and behavioral performance during scanning revealed a significant result only for testosterone and reaction times to fearful male faces ($r = -.598, p = .004$). Even after correction for mediating effects of amygdala reaction by applying partial correlations this correlation remained significant ($r = -.503, p = .024$).

3.2. Functional data

Group analyses showed bilateral amygdala activation to all presented emotions and neutral expressions for female and male posers. Besides amygdala activation, responses of bilateral fusiform gyrus, inferior occipital and frontal gyri, inferior and medial temporal regions, hippocampus and parahippocampal gyrus as well as brainstem and cerebellum emerged for all emotions and neutral expressions across all subjects (see Fig. 2).

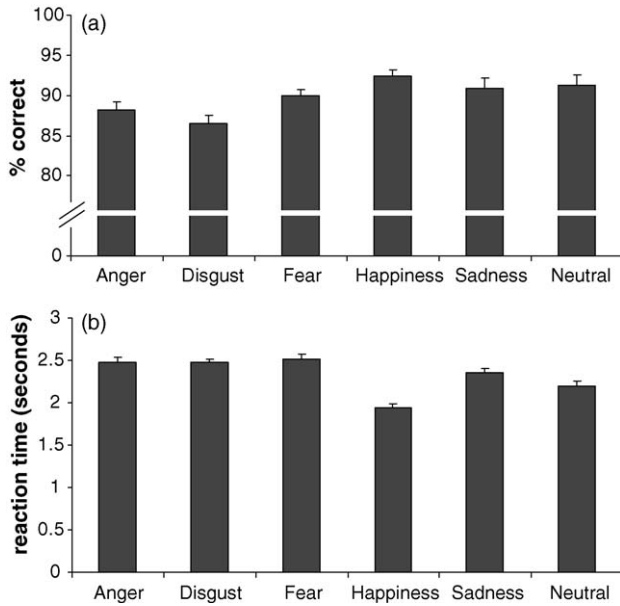


Figure 1 Illustration of behavioral performance during scanning showing (a) emotion recognition accuracy and (b) reaction times for all emotions across the male sample.

3.2.1. ROI analysis

The ROI analysis demonstrated neither a significant emotion effect ($F(3.835, 76, 699) = 2.467, p = .054$), nor a significant gender of poser effect ($F(1, 20) = 1.355, p = .258$), or a significant laterality effect ($F(1, 20) = .310, p = .584$). Only the gender of poser-by-laterality interaction reached significance ($F(1, 20) = 4.602, p = .044$), although post hoc tests remained not significant (female vs. male left amygdala: $p = .452$; female vs. male right amygdala: $p = .078$).

Correlation analyses between amygdala activation to all emotions and testosterone levels revealed a significant positive association ($r = .453, p = .039$), that was also observed for all male expressions ($r = .474, p = .030$) but not for female

expressions ($r = .354, p = .116$). Emotion-specific analyses showed significant results for amygdala response to fearful male ($r = .683, p < .001$), fearful female ($r = .649, p < .001$), and angry male faces ($r = .662, p < .001$), see Fig. 3. All other correlations did not reach significance after Bonferroni correction (all $p_s > .004$).

3.2.2. Whole slab analysis

Besides amygdala activation, responses of bilateral fusiform gyrus, inferior occipital and frontal gyri, inferior and medial temporal regions, hippocampus and parahippocampal gyrus as well as brainstem and cerebellum were present for all emotions and neutral expressions across all subjects. Results of the ANOVA with emotion and gender of poser as within-subject factors revealed no significant gender of poser main effect, no significant emotion effect, but a significant emotion-by-gender of poser interaction in the parahippocampal gyrus bilaterally (right (MNI x, y, z): 20, -18, -16, $k = 90, t = 4.08, p < .001$ uncorr.; left (MNI x, y, z): -18, -22, -18, $k = 33, t = 3.66, p < .001$ uncorr.). However, post hoc tests disentangling this significant interaction revealed no significant result for the direct comparison for each emotion applying the above-mentioned threshold ($t = 3.55, p < .001$ uncorr.).

Correlation analyses revealed significant associations of testosterone with activation of the inferior frontal gyrus only during processing of angry male (MNI x, y, z : -6, 24, -22; $t = 3.32, k = 17, p = .002$) as well as fearful male expressions (MNI x, y, z : 0, 30, -22; $t = 3.83, k = 26, p = .001$).

4. Discussion

We investigated the influence of blood testosterone levels on amygdala activation in healthy, young males performing an explicit emotion recognition task. We observed significant correlations between testosterone levels and amygdala reactivity only to angry male and fearful female and fearful male faces. These findings further highlight the specific association

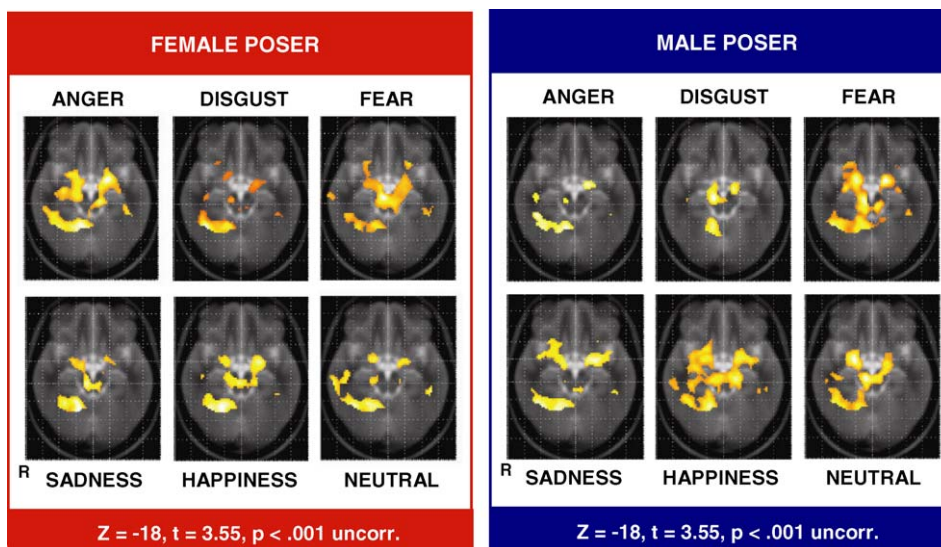


Figure 2 Results of whole-slab analysis showing activation maps of random effects analysis separately for female and male posers across the whole sample on one axial slice ($Z = -18$) comprising the amygdala (threshold: $t = 3.55, p < .001$ uncorrected).

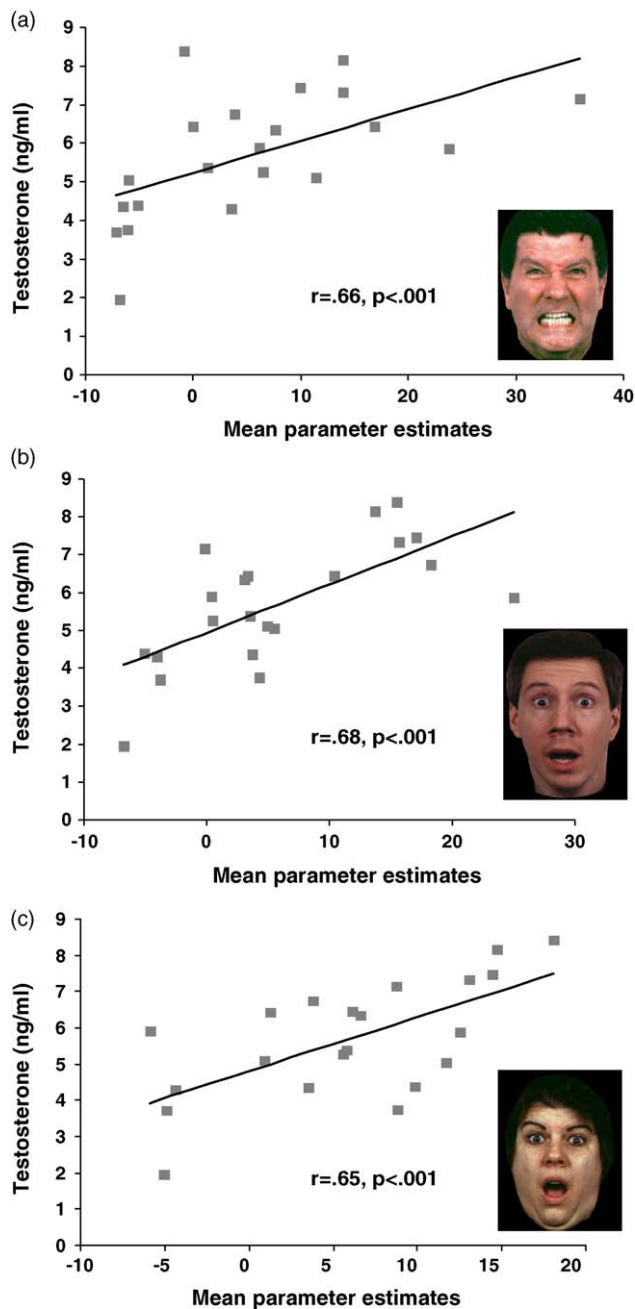


Figure 3 Results from correlation analyses depicting significant associations between testosterone levels and amygdala response (mean parameter estimates for left and right amygdala) towards angry male faces (a), fearful male faces (b), and fearful female faces (c).

of the amygdala to threat-related stimuli, as has been reported by previous neuroimaging studies (see Öhman, 2005 for review). Moreover, these results implicate a strong impact of testosterone levels on amygdala response in healthy males even within the normal range of male hormonal levels. This is the first study that has found significant correlations in males, while previous studies investigated effects of externally applied testosterone on amygdala activity in healthy females (e.g., Hermans et al., 2008; Van Wingen et al., 2008a,b). Findings from animal research

indicate that testosterone acting on the amygdala and other subcortical sites, e.g., hypothalamus, is involved in aggression regulation mainly by modulation of the vasopressin receptors (e.g., Delville et al., 1996).

Angry faces are a salient cue of socially aggressive behavior and several studies reported significant correlations between testosterone levels and aggressive behavior (e.g., Archer, 2006) or responsiveness to aggressive stimuli, mostly facial expressions of anger (Wirth and Schultheiss, 2007).

In this study, amygdala activation during recognition of fearful faces as well as reaction time toward male expressions of fear was associated with testosterone levels. Since fearful faces are stimuli related to threat and danger our results support previous findings by Wirth and Schultheiss (2007), who demonstrated an attentional shift towards threat-related stimuli with increased testosterone levels. However, these findings are somewhat contradictory to results from animal research indicating an anxiolytic effect of testosterone (Aikey et al., 2002). This effect may only be observed during emotional experience of fear (Van Honk et al., 2005) and emotion regulation but not when asked to judge and respond to emotional faces quickly.

In their totality, our findings suggest that neural processing of threat-related stimuli is related to testosterone levels, which probably reflect more automatic, subconscious or even autonomic effects of testosterone, indicated by the elevated amygdala activation with increasing testosterone levels and the significant relation between hormone levels and reaction time to fearful stimuli.

Moreover, higher testosterone levels might also modulate attention and responsiveness towards particular stimuli, which is in part reflected in the significant negative correlation between reaction time for fearful faces and testosterone levels. Hence, the higher the testosterone level the faster the correct response, which remained significant even after controlling for a mediating effect of amygdala activation by applying partial correlations. For all other emotions no such association was observed. Similarly, Van Wingen et al. (2008b) also observed a significant impact of testosterone levels on reaction times, since females showed a slower response to female faces during elevated levels of testosterone. The authors interpreted these results as a possible indication that testosterone induced a shift towards more automatic encoding and retrieval of male faces which would be important for all fertile heterosexual women. Hermans et al. (2006b) reported a reduced fear-potentiated startle response in young females after testosterone administration and Van Honk et al. (2005) observed that testosterone significantly decreased the unconscious emotional response to fearful faces. Moreover, results by Wirth and Schultheiss (2007) suggest that testosterone decreases aversion towards threat-related stimuli. Considering those results, one might speculate that when confronted with human facial expressions, testosterone prepares females and males for further behavioral action by enforcing more automatic and autonomic processes leading to attentional shifts and decrease of subconscious fear thereby facilitating approach behavior, apparent in changes in reaction times and the significant association with amygdala activation, which is also strongly connected to the fight and flight system (Kling and Brothers, 1992). Moreover, recent findings from psychiatric patients also showed a significant association of approach and avoid-

ance behavior with elevated testosterone levels in patients characterized by impulsive and aggressive behavior, e.g., antisocial personality disorder (Aromäki et al., 2002).

Analyses of the emotion recognition data revealed a significant emotion effect, with highest accuracy for happy faces, which has been shown in previous studies (e.g., Derntl et al., 2008b). Moreover, we observed a significant interaction of emotion and gender of poser: fearful male expressions and female expressions of disgust were better recognized than their corresponding counterparts. Regarding the same gender effect for fearful expressions, only one previous study reported better performance of male schizophrenia patients for fearful male expressions than fearful female expressions (Weiss et al., 2007). Mostly, studies addressing the impact of gender of poser on emotion recognition performance observed higher accuracy for female expressions in females and males (e.g., Hall and Matsumoto, 2004) probably due to a stronger expressivity of female posers (e.g., Kring and Gordon, 1998).

We did not observe an influence of testosterone levels on emotion recognition performance in our healthy males. This is not surprising given the fact that we only presented two alternatives and the performance of our participants was rather homogeneous. Many previous studies used passive viewing of emotional faces or an implicit task (e.g., gender discrimination) to investigate amygdala activation during emotional face processing. As we intended to examine the impact of testosterone on the role of the amygdala during discrimination/recognition of emotions in facial expressions we turned to this specific task. Even a matching task (using one emotional face as target and two alternative faces as responses, one depicting the same emotion) is not adequate for this purpose, since it does not require the explicit categorization of the face but rather a choice based on similarity. It could therefore be that the subject is not able to name the emotion but nevertheless finds the correct emotional face corresponding to the target.

Explicit emotion recognition tasks have rarely been applied in affective neuroscience but possess the opportunity to correlate behavioral performance (recognition accuracy and reaction time) with neural correlates providing new insights in the relation between neural activation and behavior.

Despite the limitations associated with using only two alternatives as response categories we are not aware of other practical ways to examine the neural correlates of this basic social ability. In our opinion response devices offering more than two or three possibilities in fMRI settings implicate other disadvantages such as a higher error response rates due to a lack of visual control of their responses. Furthermore, it introduces other confounding factors such as cognitive processes in form of a higher working memory load.

Several methodological constraints have to be considered in interpreting our results. Repeated testing within the same subject group would have enabled a more detailed analysis of fluctuations of testosterone levels and the influence on amygdala activation. Moreover, analysis of interaction effects of testosterone with cortisol would have been interesting, as testosterone down-regulates the hypothalamic-pituitary-adrenal axis leading to chronically decreased cortisol (Viau, 2002), which in turn has been linked to higher aggression in animal research (Kalin, 1999). We did not

measure aggressiveness or current mood of subjects which might also influence hormone levels and thus neural activation and should be considered in future studies.

We also did not investigate the influence of gaze and used only expressions with direct gaze. However, several studies have reported a significant impact of gaze on amygdala activation in particular during processing of angry and fearful faces (e.g., Adams et al., 2003), thus future studies should include gaze of posers as a variable and highlight its association with testosterone levels.

In this study we explored the association between testosterone levels and amygdala activation to emotional facial expressions in healthy young men and relied on an optimized protocol for mapping the amygdala, thereby accepting restricted coverage of other regions essential for emotion processing, e.g., inferior frontal gyrus, insula or anterior cingulate cortex. Despite its key role in the neural network underlying emotional behavior, the amygdala is just one node and interacts with several other brain regions. Here, we also observed a significant correlation between testosterone levels and neural activation of the inferior frontal gyrus. Future studies using whole brain coverage might usefully assess the impact of hormone concentration on these sites as well as the functional connectivity within the emotional networks.

We conclude that testosterone levels affect amygdala activation and also behavioral responses to emotion, but particularly to threat-related emotions in healthy young males. Our results suggest a strong association between neuroendocrine status, amygdala activation and emotion recognition performance. This might enable a faster and deeper processing of angry and fear related stimuli, with possible evolutionarily significant behavioral effects. Our results also clearly demonstrate that sex hormone concentration is a relevant factor when investigating neural correlates of emotion processing and could help to explain intra- and inter-subject variability in behavioral and neural responses.

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Conflict of interest

All authors declare NO conflict of interest.

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