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Research report

Endogenous testosterone levels are associated with neural activity in men with schizophrenia during facial emotion processing

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HIGHLIGHTS

- Testosterone related to neural activity during emotion processing in schizophrenia.
- Testosterone not related to neural activity during emotion processing in healthy men.
- Testosterone levels may interfere with social function in schizophrenia.

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ABSTRACT

Growing evidence suggests that testosterone may play a role in the pathophysiology of schizophrenia given that testosterone has been linked to cognition and negative symptoms in schizophrenia. Here, we determine the extent to which serum testosterone levels are related to neural activity in affective processing circuitry in men with schizophrenia. Functional magnetic resonance imaging was used to measure blood-oxygen-level-dependent signal changes as 32 healthy controls and 26 people with schizophrenia performed a facial emotion identification task. Whole brain analyses were performed to determine regions of differential activity between groups during processing of angry versus non-threatening faces. A follow-up ROI analysis using a regression model in a subset of 16 healthy men and 16 men with schizophrenia was used to determine the extent to which serum testosterone levels were related to neural activity. Healthy controls displayed significantly greater activation than people with schizophrenia in the left inferior frontal gyrus (IFG). There was no significant difference in circulating testosterone levels between healthy men and men with schizophrenia. Regression analyses between activation in the IFG and circulating testosterone levels revealed a significant positive correlation in men with schizophrenia ($r = .63$, $p = .01$) and no significant relationship in healthy men. This study provides the first evidence that circulating serum testosterone levels are related to IFG activation during emotion face processing in men with schizophrenia but not in healthy men, which suggests that testosterone levels modulate neural processes relevant to facial emotion processing that may interfere with social functioning in men with schizophrenia.

1. Introduction

Impaired social functioning is a hallmark of schizophrenia that is gaining increasing attention. Poor social functioning in individuals with schizophrenia has been linked to abnormal processing of facial emotions [1]. A meta-analysis reported a significant positive correlation between severity of negative symptoms and facial

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emotion perception impairment in schizophrenia [2]. People with schizophrenia also have difficulty identifying and discriminating among different facial expressions [3], in particular those of negative valence [4,5].

The underlying neural network of this impairment is not fully understood although functional neuroimaging studies show abnormalities in the limbic system and frontal cortex when people with schizophrenia are exposed to affective stimuli [5–7]. Facial affect processing has been frequently studied as a method of exploring the neural substrates of social impairment in schizophrenia. In functional Magnetic Resonance Imaging (fMRI) studies, people with schizophrenia predominantly display hypoactivation in regions normally recruited by healthy individuals during the processing of facial emotions. One study showed that individuals with schizophrenia had diminished limbic response in the left amygdala and bilateral hippocampus during facial emotional discrimination relative to healthy adults [6]. In another study, people with schizophrenia showed significantly less activation than healthy controls in response to angry expressions in the inferior frontal gyrus (IFG), putamen and cerebellum [8]. The first part of the present study was designed to use fMRI to confirm the neural activation patterns underlying the identification of angry compared to non-threatening facial expressions in a sample of men and women with schizophrenia relative to healthy men and women.

Steroid hormones and particularly testosterone have been implicated in emotion processing. Studies have reported both positive and negative associations between testosterone levels and emotion-related neural activation in healthy people. Derntl et al. [9] found a significant positive correlation in healthy men between endogenous testosterone and amygdala response to fearful and angry facial expressions, but no correlation with non-threatening expressions such as sadness and happiness. Similar findings have been reported in healthy women whose endogenous testosterone levels correlated positively with amygdala activity during the processing of fearful and angry faces [10]. Stanton et al. [11] found that endogenous testosterone levels were negatively correlated with amygdala BOLD activity and positively correlated with ventromedial prefrontal cortex BOLD activity during the processing of angry faces; however, both findings occurred only in healthy males. When middle-aged women were given a single dose of testosterone, Van Wingen et al. [10] reported positive correlations between exogenous testosterone and activity in the amygdala and superior frontal cortex along with a negative correlation between exogenous testosterone and neural activity in the orbitofrontal cortex and occipital gyrus in response to angry and fearful facial stimuli. Another study reported a significant increase in neural activity in the amygdala and hypothalamus while viewing angry faces after healthy female participants received a .5 ml dose of testosterone [12]. Altogether, these findings generally suggest that endogenous testosterone modulates neural activity during processing of negative facial emotion in healthy people, particularly males, although the exact mechanism is unknown and some conflicting results have been reported.

Steroid hormones may play a role in symptom onset, severity and the disease process associated with schizophrenia and have been linked to both cognition and negative symptoms [13–15]. However, few studies examining a possible relationship between testosterone and emotion processing in people with schizophrenia have been reported. Previous work by our lab demonstrated a strong inverse association between serum testosterone levels and activation of the bilateral middle frontal gyrus and left insula during an emotional word inhibition task in men with schizophrenia, but not in healthy men [16], suggesting that testosterone may play a moderating role in the frontal hypoactivity observed in schizophrenia. In the second part of the present study we sought to determine the extent to which serum testosterone levels are related to neural activity in emotion processing circuitry in men with schizophrenia compared to healthy men, using a region of interest approach.

We predicted abnormal prefrontal and amygdala activity in men and women with schizophrenia during the processing of emotional faces. Given that most studies report a positive relationship between neural activity during processing of angry faces and testosterone levels in healthy men and women and abnormal neural activity during affective facial identification in schizophrenia, we predicted that the positive relationship between neural activity and circulating testosterone levels in healthy men during affective facial processing would be disrupted in men with schizophrenia.

2. Material and methods

2.1. Effects of emotional faces on neural activity in men and women

2.1.1. Participants

The study sample included 27 people with schizophrenia or schizoaffective disorder (17 male, 10 female) and 37 healthy comparison participants (20 male, 17 female). Patients were recruited from a national television documentary, the Kiloh Center at the Prince of Wales Hospital and other clinics from the South Eastern Sydney and Illawarra Area Health Service. All patients were between 21 and 51 years of age and were receiving antipsychotic medication for at least 1 year prior to taking part in the study. Clinical diagnostic interviews using the Structured Clinical Interview for DSM-IV (SCID) [17] were conducted by a trained psychologist or psychiatrist. Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) [18].

Healthy comparison participants between 20 and 42 years of age were recruited from the local community via advertisements. Exclusion criteria for all participants included substance abuse or dependency within the past 5 years, seizures, central nervous system infection, uncontrolled diabetes or hypertension, a history of neurological illness, head injury with loss of consciousness and structural brain abnormalities as assessed by MRI scan. Additional exclusion factors were a concurrent DSM-IV Axis I disorder in patients and any history of DSM-IV Axis I disorder in healthy controls or their siblings.

All participants were assessed with the Wechsler Test of Adult Reading (WTAR) [19] to obtain an estimate of (premorbid) intellectual functioning in patients and a four subtest version of the Wechsler Adult Intelligence scale, 3rd edition (WAIS-III) [20] comprised of the Arithmetic, Digit Symbol, Similarities and Picture Completion subtests to assess current intellectual functioning. The study procedures were approved by the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service Ethic Committees. All participants provided written informed consent prior to participation in the study and received reimbursement for their time and expenses.

2.1.2. Facial stimuli and procedure

Participants were presented with 60 color pictures of human faces depicting emotional expressions (12 happy, 12 sad, 12 angry, 12 fear, 12 neutral) that alternated with a fixation cross [6]. Each face was presented for 5.5s and on presentation, participants were required to choose the emotion displayed using a button box. Given that angry facial expressions more robustly elicit differential neural activity in schizophrenia relative to controls, for the purpose of this study, we focused on neural activation for angry versus non-threat (happy and neutral) faces.

2.1.3. Image acquisition

Echoplanar MR brain images were acquired using a three Tesla Phillips Achieva MRI scanner with an eight channel bird-cage