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Effects of testosterone on attention and memory for emotional stimuli in male rhesus monkeys

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Summary Increasing evidence in humans and other animals suggests that testosterone (T) plays an important role in modulating emotion. We previously reported that T treatment in rhesus monkeys undergoing chemically induced hypogonadism results in increased watching time of videos depicting fights between unfamiliar conspecifics (Lacreuse et al., 2010). In the current study, we aimed to further investigate the effect of T manipulations on attention and memory for emotional stimuli in male rhesus monkeys. Six males (7 years old) were administered Depot Lupron to suppress endogenous T levels and treated with either testosterone enanthate (TE, 5 mg/kg) or oil, before crossing over to the alternate treatment. Animals were tested for 16 weeks on two computerized touchscreen tasks with both social and nonsocial emotional and neutral stimuli. The Dot-Probe task was used to measure attention, and the Delayed-Non-Matching-to-Sample task with a 1 s delay (DNMS) was used to measure recognition memory for these stimuli. Performance on the two tasks was examined during each of four month-long phases: Baseline, Lupron alone, Lupron + TE and Lupron + oil. It was predicted that T administration would lead to increased attention to negative social stimuli (i.e., negative facial expressions of unfamiliar conspecifics) and would improve memory for such stimuli. We found no evidence to support these predictions. In the Dot-Probe task, an attentional bias towards negative social stimuli was observed at baseline, but T treatment did not enhance this bias. Instead, monkeys had faster response times when treated with T compared to oil, independently of the emotional valence or social relevance of stimuli, perhaps reflecting an enhancing effect of T on reward sensitivity or general arousal. In the DNMS, animals had better memory for nonsocial compared to social stimuli and showed the poorest performance in the recognition of positive facial expressions. However, T did not affect performance on the task. Thus, even though monkeys were sensitive to the social relevance and emotional valence of the stimuli in the two tasks, T manipulations had no effect on attention or memory for these stimuli. Because habituation to the stimuli may have mitigated the effect of treatment in the attentional task, we suggest that T may increase attentional biases to negative social stimuli only during early exposure to the stimuli with

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acute treatment or when stimuli are highly arousing (i.e., dynamically presented) with chronic treatment. In addition, the data suggest that T does not enhance working memory for emotional stimuli in young male macaques.

1. Introduction

The dramatic drop in sex hormones experienced by women during menopause has inspired a substantial body of literature regarding the effects of estrogen deprivation and hormone replacement (for a recent review, see Shifren and Schiff, 2010). Less literature is available regarding age-related testosterone (T) decline and the effects of T replacement in men. Endogenous T levels peak around the age of 30 in men and steadily decline thereafter, to the extent that serum T levels have been reported to be 50% lower in 80-year-old as compared to 30-year-old men (Harman et al., 2001). This substantial decline in T levels throughout adult life has well documented effects on reproductive behavior (Baum and Crespi, 2007) and some aspects of cognitive function (Moffat, 2005; Janowsky, 2006; Beauchet, 2006; Cherrier, 2009). However, the impact of hypogonadism on emotion has received considerably less attention. With many men being potential candidates for T replacement therapy, it is important to elucidate the effects of T on emotional processing.

Among primates, androgen receptors are present in various brain regions which play an important role in emotion, such as the amygdala, hypothalamus and hippocampus (Clancy et al., 1992; Choate et al., 1998; Abdelgadir et al., 1999). There is also evidence to suggest that T affects neural morphology (Cooke, 2006; Hajszan et al., 2008) and neural activity (in some cases resulting in behavioral changes) in these areas (Derntl et al., 2009; Stanton et al., 2009; Manuck et al., 2010). Thus, T may influence emotional processing by modulating the function of these brain regions.

A few studies have provided evidence for a relationship between T levels and selective attention to threatening social stimuli. The pictorial emotional Stroop task, in which pictures of emotional faces are washed over in colors such as red or green, requires human participants to name the color of the emotional face as quickly as possible. Both men and women with higher salivary T showed significantly greater selective attention (compared to those with lower T levels) to angry faces, as evidenced by greater interference (longer reaction time) in color naming on these trials (van Honk et al., 1999). Additionally, men who showed greater selective attention to angry faces also showed greater T increase following their exposure to emotional faces compared to those who did not exhibit this attentional bias (van Honk et al., 2000). Others have reported that higher morning T in both men and women predicts greater attention to angry faces in a sub-threshold emotional Stroop task (Wirth and Schultheiss, 2007). Importantly, these studies failed to examine the relationship between T and attention to *nonsocial* negative stimuli. Therefore, further research is necessary to fully comprehend the extent to which T biases attention to threat.

Additionally, while these correlational studies discussed above suggest a link between T and attention to negative stimuli, they do not establish causal relationships. We previously found that, following suppression of endogenous T, adult male rhesus monkeys who received T treatment watched negative videos involving fights between unfamiliar conspecifics for significantly longer periods of time than when they received a placebo (Lacreuse et al., 2010). T treatment did not affect watching time for neutral or positive videos. However, the negative videos (fight scenes) included a greater number of individuals and involved more physical action compared to the positive (grooming scenes) and neutral (sleeping scenes) videos, calling for additional control to understand the precise effects of T on attention to negative/threatening stimuli.

If T does increase attention to threatening stimuli, it may also improve memory for such stimuli. Many studies have shown a positive or curvilinear relationship between T levels and working memory in humans (Janowsky et al., 2000; Moffat, 2005; Beer et al., 2006; Cherrier et al., 2007), and similar findings have been reported for the effects of T on spatial working memory in rats (Sandstrom et al., 2006; Spritzer et al., 2011) but there is a paucity of literature regarding T and emotional working memory. It is well established in humans that emotional content tends to be better remembered than neutral content in long-term memory (e.g., Cahill and McGaugh, 1995) and that the emotional enhancement of memory is correlated with increased amygdalar and hippocampal activity (McGaugh et al., 1993; Cahill et al., 1995; Phelps, 2006; Sommer et al., 2008). Recent evidence in humans also suggests that T affects amygdalar activation to emotional stimuli. For example, endogenous T levels were positively related to the degree of amygdalar response to fearful faces (Derntl et al., 2009) and angry faces (Stanton et al., 2009) and predicted greater activation of the dorsal amygdala (Manuck et al., 2010) in healthy young men. Lower androgen levels in women have been associated with reduced amygdalar reactivity to angry and fearful faces and acute T administration resulted in increased amygdalar reactivity to these faces (van Wingen et al., 2009). Similarly, T administration enhanced reactivity of the amygdala to presentations of angry (vs. happy) faces in another study in women (Hermans et al., 2008). Thus it is likely that T has an enhancing effect on emotional memory through its action in the amygdala. However, it is important to note that some literature suggests that emotional content does not have the same robust effect on working memory (e.g., Kensinger and Corkin, 2003).

Much of the existing evidence regarding the effects of exogenous T on attention to emotional stimuli has been collected in either rodent models or human females, leaving unanswered pressing questions regarding the effects of T on emotional processing in healthy human males. Because of potential health risks associated with T treatment in men (Liverman and Blazer, 2004), nonhuman primate models are useful to investigate T effects on emotional processing in healthy males. Given that rhesus monkeys show similarities