Neuropsychologia 73 (2015) 108–115

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Neuroticism modulates the effects of intranasal vasopressin treatment on the neural response to positive and negative social interactions

Chunliang Feng [a,f], Ashley C. DeMarco [g], Ebrahim Haroon [b], James K. Rilling [a,b,c,d,e,*]

[a] Department of Anthropology, Emory University, United States
[b] Department of Psychiatry and Behavioral Sciences, Emory University, United States
[c] Center for Behavioral Neuroscience, Emory University, United States
[d] Yerkes National Primate Research Center, Emory University, United States
[e] Center for Translational Social Neuroscience, Emory University, United States
[f] State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, China
[g] Department of Psychology, University of Kansas, United States

ARTICLE INFO

Article history:
Received 26 January 2015
Received in revised form
12 April 2015
Accepted 7 May 2015
Available online 12 May 2015

Keywords:
Neuroticism
Oxytocin
Vasopressin
fMRI
Cooperation

ABSTRACT

Neuroticism is a fundamental personality trait associated with proneness to feel negative affect. Here we ask how Neuroticism influences the neural response to positive and negative social interactions and how Neuroticism modulates the effect of intranasal oxytocin (OT) and vasopressin (AVP) on the neural response to social interactions. In a double-blind, placebo-controlled study, 153 male participants were randomized to receive 24 IU intranasal OT, 20 IU AVP or placebo. Afterwards, they were imaged with fMRI while playing an iterated Prisoner's Dilemma Game. On a different day, subjects completed the NEO personality inventory to measure Neuroticism. Neuroticism was positively correlated with the neural response to negative social interactions in the anterior cingulate cortex/medial prefrontal cortex and with the neural response to positive social interactions in the insula, indicating that Neuroticism modulates neuropsychological processing of both negative and positive social interactions. Neuroticism did not modulate the effect of intranasal OT treatment on the neural response to either positive or negative social interactions. On the other hand, AVP treatment significantly interacted with Neuroticism to modulate the BOLD response to both positive and negative social interactions. Specifically, AVP increased anterior cingulate cortex/medial prefrontal cortex and lateral temporal lobe responses to negative social interactions to a greater extent in participants scoring high rather than low on Neuroticism. AVP also increased the insula response to positive social interactions to a greater extent in participants scoring high rather than low on Neuroticism. These results imply that AVP may increase emotion regulation in response to negative social interactions and the salience of positive social interactions to a greater extent in individuals high compared to low in Neuroticism. The current findings urge caution against uniform clinical application of nonapeptides and suggest that their efficacy may vary as a function of personality.

1. Introduction

Neuroticism is a fundamental personality trait associated with proneness to feel negative affect (Costa and McCrae, 1992). Individuals high in Neuroticism are more prone to perceive rejection and feel less satisfaction and intimacy in romantic relationships (Downey and Feldman, 1996; White et al., 2004). Furthermore, individuals high in Neuroticism report heightened grief after the loss of a known other (Bailley, 1999). These findings suggest Neuroticism is associated with greater perceived salience of social aversiveness (Eisenberger and Lieberman, 2005). Accordingly, a growing body of neuroimaging studies has demonstrated that Neuroticism shows a positive correlation with the neural response to negative stimuli in brain regions involved in salience and emotion processing, such as the insula, striatum and amygdala (Brühl et al., 2011; Harenski et al., 2009; Paulus et al., 2003), as well as regions implicated in emotion regulation, such as dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC) and lateral temporal lobe (Canli et al., 2001; Haas et al., 2008; Harenski et al., 2009; Jimura et al., 2009; Servaas et al., 2013). Notably, Neuroticism is also positively correlated with the neural response to positive stimuli in the

* Correspondence to: Department of Anthropology, Emory University, 1557 Dickey Drive, Atlanta, GA 30322, United States.
E-mail address: jrillin@emory.edu (J.K. Rilling).

http://dx.doi.org/10.1016/j.neuropsychologia.2015.05.004
0028-3932/

striatum (Brühl et al., 2011; Schaefer et al., 2011), suggesting that Neuroticism is associated with enhanced salience of both negative and positive stimuli.

In addition to personality traits, there are known biological influences on human social-emotional functioning and related brain activity. For example, the neuropeptide oxytocin (OT) enhances trust behavior (Baumgartner et al., 2008), increases attention to and memory for positive stimuli (Domes et al., 2013; Guastella et al., 2008), and augments the neural response to positive social events in brain regions associated with salience and reward processing (Groppe et al., 2013; Rilling et al., 2012; Scheele et al., 2013). Further, OT decreases cortisol stress responses induced by negative social interactions (Ditzen et al., 2009; Linnen et al., 2012), and attenuates amygdala responses to negative stimuli (Kirsch et al., 2005; Petrovic et al., 2008). On the other hand, AVP may play a role in inter-male aggressive communication such that AVP induces agonistic facial motor patterns of male participants in response to the faces of unknown men and attenuates perceptions of the friendliness of those faces (Thompson et al., 2004, 2006). Additionally, intranasal administration of AVP increased neural response to negative faces in brain areas important in salience processing (e.g., amygdala) (Brunnlieb et al., 2013) and emotional regulation (e.g., mPFC) (Zink et al., 2010). Nevertheless, AVP is not always anxiogenic, and has also been linked with affiliative, prosocial behavior in some contexts (Goodson and Thompson, 2010). For example, intranasal vasopressin increased empathic concern in response to emotional videos among individuals who received higher levels of paternal warmth (Tabak et al., 2015). Furthermore, we previously showed that intranasal AVP treatment made men more likely to reciprocate cooperation from other men in an iterated PD game (Rilling et al., 2012). Finally, AVP treatment has been shown to enhance memory for not only angry, but also happy faces in humans (Guastella et al., 2010). Therefore, previous studies suggest that AVP may facilitate the processing of both negative and positive events/stimuli.

Importantly, however, the effects of intranasal nonapeptide treatments on human social-emotional functioning are not ubiquitous, but are heterogeneous across individuals (Bartz et al., 2011). For instance, OT decreased cortisol stress responses especially among participants low rather than high in emotional regulation abilities (Quirin et al., 2011). In addition, intranasal administration of OT normalizes hyperactivity of amygdala and mPFC to negative stimuli in individuals with generalized social anxiety disorder, whereas there were no effects of OT on the activity of amygdala and mPFC in the control group (Labuschagne et al., 2010, 2012). These findings suggest that OT is better able to attenuate the salience of negative events among individuals low in socia–emotional functioning. On the contrary, the effects of OT in enhancing salience of positive events might be blunted in individuals exhibiting low social-emotional abilities (Scheele et al., 2014). There has been much less research on the effects of intranasal AVP in human social-emotional cognition and related brain functions, and to the best of our knowledge no study has yet investigated how effects of AVP are modulated by dispositional personality traits.

Here, we build on previous studies by investigating how Neuroticism modulates the neural response to real-time, experienced positive and negative social interactions in the context of an iterated Prisoner's Dilemma (PD) game and how Neuroticism interacts with intranasal administration of OT and AVP. The iterated PD game is a model for relationships based on reciprocal altruism, or the reciprocal exchange of favors. In the game, two players chose to either cooperate with each other or not. Previous studies in our lab have demonstrated that reciprocated cooperation (CC) is associated with activation in brain regions that have been linked with reward processing such as striatum as well as high levels of positive affect (Rilling et al., 2002); whereas unreciprocated cooperation (CD) is associated with activation in insula and amygdala as well as high levels of negative affect (Rilling et al., 2007, 2008).

In light of previous findings, we expected that individuals scoring high on Neuroticism (as compared to those scoring low on Neuroticism) would show (a) enhanced neural activation to negative social interactions in brain regions important in salience processing (e.g., amygdala, insula) and emotion regulation (e.g., dlPFC, ACC, mPFC) and (b) enhanced neural activation to positive social interactions in areas involved in reward or salience processing (e.g., striatum, insula). Regarding the interaction between intranasal nonapeptide treatments and Neuroticism, we expected that OT would facilitate neural responses to positive social interactions among individuals low in Neuroticism (high social emotional functioning) more so than those high in Neuroticism (low social emotional functioning). We also expected that OT would attenuate the neural response to negative social interactions among individuals high in Neuroticism (low social emotional functioning) more so than those low in Neuroticism (high social emotional functioning). Finally, AVP might increase neural responses to both positive and negative social interactions among individuals low in Neuroticism more so than those high in Neuroticism, given that individuals scoring high in Neuroticism might show strong neural responses to positive and negative events even at baseline (i.e., the placebo group) and effects of AVP would be limited in those individuals. Alternatively, AVP treatment might have additive effects with Neuroticism such that the functions of AVP in enhancing neural response to positive and negative events would be stronger among individuals high in Neuroticism than those low in Neuroticism.

2. Material and methods

2.1. Subjects

153 men from the Emory University community between the ages of 18 and 22 (mean age=20.7 years) were randomized to receive intranasal OT (n=50), intranasal AVP (n=49), or intranasal placebo (n=54). All subjects gave written informed consent, and the study was approved by the Emory University Institutional Review Board and the U.S. Food and Drug Administration. Fourteen men (OT n=5, AVP n=4, and placebo n=5) were excluded from the neuroimaging analysis due to excessive motion ($>$1.5 mm) (n=8), missing data (n=2), abnormal brain anatomy (n=1) or to not completing the NEO-PI-RI questionnaire (n=3).

2.2. Behavioral procedures

2.2.1. Administration of OT, AVP or placebo

Both experimenters and subjects were blind to the treatment subjects received. All solutions were administered intranasally. The OT group self-administered 24 IU oxytocin (Syntocinin-Spray, Novartis), and the AVP group self-administered 20 IU of AVP (American Reagent Laboratories, Shirley, NY, USA). In each case, this required 10 nasal puffs to administer 1 ml of solution. The placebo group self-administered 10 nasal puffs of either OT placebo or AVP placebo (both including all ingredients, i.e., preservatives, without the active pharmacological substance). Half of the placebo subjects received OT placebo and half received AVP placebo. Subjects were instructed to place the nasal applicator in one nostril and depress the lever until they felt a mist of spray in the nostril, to then breathe in deeply through the nose, and afterwards to place the applicator in the other nostril and repeat the process.