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Oxytocin receptor gene polymorphism modulates the effects of social support on heart rate variability

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ABSTRACT

A large body of empirical research has demonstrated stress-buffering effects of social support. However, recent studies suggest that genetic variation of the oxytocin system (specifically, a common single nucleotide polymorphism, rs53576, of the oxytocin receptor gene) modulates the efficacy of social support. The timing and neurobiological basis of this genetic modulation were investigated using a standardized, laboratory-based psychological stress procedure (Trier Social Stress Test for Groups, TSST-G). To index potential stress buffering effects of social support mediated by the oxytocin system, heart rate variability (HRV) was obtained before and during the TSST-G from 40 healthy participants. Results indicate that social support is associated with higher HRV only in G allele carriers. Specifically, social support increased heart rate variability during direct social interaction and only in individuals with at least one copy of the G allele of rs53576. These findings support the idea that the stress-attenuating effects of social support are modulated by genetic variation of the oxytocin system.

1. Introduction

The powerful influence of social support as a protective factor for maintaining and restoring health is well established (Cohen, 1988; Uchino, Cacioppo, & Kiecolt-Glaser, 1996; Weihs et al., 2005). Converging evidence from both laboratory-based and epidemiological research suggests that one mechanism through which social support exerts its influence on health is by attenuating physiological stress reactivity (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kirschbaum, Klauer, Filipp, & Hellhammer, 1995; Lepore, Allen, & Evans, 1993).

Although social interactions have stress-attenuating effects for most individuals, empirical research has revealed individual differences in these effects (Chen et al., 2011; Ditzen et al., 2008; Kim, Sherman, & Taylor, 2008; Taylor, Welch, Kim, & Sherman, 2007). A growing body of research suggests that genetically-based differences in the oxytocin system may contribute to these individual differences. The fact that oxytocin exhibits pro-social and stress-attenuating effects (Heinrichs, von Dawans, & Domes, 2009; Kumsta & Heinrichs, 2013; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011), makes this neuropeptide a plausible mediator of the stress-buffering effects of social support. Additional support comes from research showing that in combination with social support, oxytocin attenuates autonomic stress responses (Heinrichs et al., 2003; Meyer-Lindenberg et al., 2011).

Research on genetic variations of the oxytocin receptor (*OXTR*), through which oxytocin exerts a range of effects throughout the

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body and brain (Gimpl & Fahrenholz, 2001; Inoue et al., 1994), seems especially promising. One of the most-studied variations of *OXTR* is the single nucleotide polymorphism (SNP) rs53576 (G/A). Recent studies have linked this SNP to variability in both social behaviour (Bakermans-Kranenburg & van Ijzendoorn, 2008; Meyer-Lindenberg et al., 2011) and stress reactivity (Kumsta & Heinrichs, 2013; Norman et al., 2012; Rodrigues, Saslow, Garcia, John, & Keltner, 2009). Specifically, the A allele has been associated with reduced positive affect (Lucht et al., 2009), reduced maternal sensitivity (Bakermans-Kranenburg & van Ijzendoorn, 2008), and reduced empathic accuracy (Rodrigues et al., 2009). The A allele has also been associated with a higher risk for autism spectrum disorder (e.g., Wu et al., 2005) and depression (e.g., Saphire-Bernstein et al., 2011), both of which are associated with social functioning deficits.

Given that rs53576 has been shown to predict both stress buffering and prosocial behaviour, this SNP may also contribute to individual differences in the stress-buffering effects of social support. In fact, research from our lab showed that only individuals with at least one copy of the G allele of rs53576 displayed lower cortisol responses to stress following social support, relative to individuals of the same genotype receiving no social support (Chen et al., 2011). However, because cortisol reactions can be measured only with a substantial delay (in the range of 15–20 min) after the actual stressful event, the precise timing of the interaction between social support and rs53576 remains unclear.

Relevant to the search for the physiological locus of the aforementioned modulating effect of rs53576 is research in non-human mammals demonstrating a multilateral distribution of the oxytocin receptor in various brain regions that are associated with central nervous system (CNS) control of stress, including the amygdala, the paraventricular nucleus (PVN), nucleus tractus solitarious (NTS), the dorsal motor nucleus of the vagus (DMX), and the nucleus ambiggus (NA) (Coote, 2013; Higa, Mori, Viana, Morris, & Michelini, 2002; Landgraf & Neumann, 2004; Luiten, Ter Horst, Karst, & Steffens, 1985). This is consistent with the possibility that variants of rs53576 could modulate the stress-buffering effects of social support at a central nervous system level.

Further support comes from research in non-human mammals showing that oxytocin modulates amygdala-mediated activation of the peripheral stress reaction (Viviani et al., 2011). However, none of the previous studies directly investigated the effects of the SNP rs53576 in combination with social support on CNS stress regulation. The use of heart rate variability (HRV) as an indicator of differences in stress regulation via recruitment of the parasympathetic system may help bridge this gap in knowledge.

Empirical evidence suggests that CNS stress regulation can be indexed by vagal functioning level (Thayer & Lane, 2009). Because the vagus nerve modulates the heart rate on a time scale of milliseconds, high frequency changes in heart rate, known as HRV, are a valid index of parasympathetic activation level (Thayer, Hansen, & Johnsen, 2008) and therefore for CNS stress regulation (Friedman & Thayer, 1998; Gianaros, Van der Veen, & Jennings, 2004; Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012), at a high temporal resolution. A large body of evidence associating positive social interactions with increased HRV (Kok & Fredrickson, 2010; Maunder et al., 2012; Smith et al., 2011) further illustrates the usefulness of this index in the present research design. The basic data used for calculating HRV is the sequence of time intervals between consecutive heart beats, also known as inter-beat intervals (for more information on HRV, see Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Furthermore, stimulation of oxytocin neurons has been shown to induce heart rate slowing (bradycardia) and increased vagal tone (Higa et al., 2002; Rogers & Hermann, 1986). Importantly, it has been shown that these oxytocin neurons are associated with stress buffering in that they are more active during stressful events and thus serve to reduce the impact of such events by lowering heart rate via increased vagal tone (Higa et al., 2002), which strongly suggests the capability of HRV to index stress-buffering effects of social interactions mediated by oxytocin. The idea that oxytocin may play a role in modulating outflow of vagal efferent activity on a central nervous level was proposed more than a decade ago within the framework of Polyvagal Theory (Carter, 1998; Porges, 1997). Notably, however, no studies have yet examined the association between naturally-occurring individual differences in the functioning of the oxytocin system and measures of cardiac vagal outflow as indexed by HRV in the context of social stress buffering.

Therefore, the present study investigated the CNS basis and the timing of the interaction of social support and rs53576 on stress reactivity. We predicted that individuals with at least one copy of the G allele would benefit more from social support when anticipating a stressor than individuals homozygous for the A allele of rs53576, and that this difference would be indexed by elevated HRV. We also investigated whether this difference would be most apparent during the period of direct social interaction, as suggested by research on the stress-buffering effect of oxytocin on cardiac autonomic control.

2. Material and methods

2.1. Participants

Students at the University of Freiburg, Germany were recruited to participate in a study about "behavior in job interviews." Given previous research on sex differences in stress-buffering effects of social support (e.g. Kirschbaum et al., 1995), only male students and female supporters were included in the study sample. Exclusion criteria included prior participation in a stress induction study, studying psychology, chronic or acute illness, current or previous psychiatric treatment, smoking more than five cigarettes a day, medication use, or substance abuse. Students were only allowed to participate in the study if they were able to bring a close female supporter (e.g., friend, romantic partner, roommate) to the experimental session. Participants were randomly assigned into two groups. The first group (*social support condition*) brought their social supporter with them, and the second group (*no social support condition*) came alone. The participants were told to refrain from drug, medication, caffeine and alcohol use for 24 h before the session. They were instructed to eat as they usually do and then abstain from food two hours prior the session. All participants provided written informed consent and were paid 25 Euros for their participation. Female supporters received a small gift for their participation. The study was approved by the Institutional Review Board of the University of Freiburg.

The sub-sample analysed for the present investigation was stratified on the basis of *OXTR* genotype. In the large sample ($N = 203$), there were twenty-nine individuals with the AA genotype, nine of whom had to be excluded because of artefacts in the heart rate recording produced by excessive movements. All twenty individuals with the AA genotype with useable heart rate data were included in the current analyses, and thus, a sample of exactly twenty G allele carriers (GG or GA) was also selected from the large sample. Specifically, 10 GG allele carriers (social support: n = 5; no social support: n = 5) and 10 GA carriers (social support: n = 5; no social support: n = 5) were chosen from the large sample using a random number generator. The sole inclusion criterion for the G carriers was an evaluable heart rate recording.