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Disruption of social bonds induces behavioral and physiological dysregulation in male and female prairie voles

Neal McNeal [a], Melissa-Ann L. Scotti [a,b], Joshua Wardwell [a], Danielle L. Chandler [a], Suzanne L. Bates [a], Meagan LaRocca [a], Diane M. Trahanas [a], Angela J. Grippo [a,*]

[a] Department of Psychology, Northern Illinois University, United States
[b] Department of Psychiatry and Brain Body Center, University of Illinois at Chicago, United States

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ABSTRACT

The social disruption of losing a partner may have particularly strong adverse effects on psychological and physiological functioning. More specifically, social stressors may play a mediating role in the association between mood disorders and cardiovascular dysfunction. This study investigated the hypothesis that the disruption of established social bonds between male and female prairie voles would produce depressive behaviors and cardiac dysregulation, coupled with endocrine and autonomic nervous system dysfunction. In Experiment 1, behaviors related to depression, cardiac function, and autonomic nervous system regulation were monitored in male prairie voles during social bonding with a female partner, social isolation from the bonded partner, and a behavioral stressor. Social isolation produced depressive behaviors, increased heart rate, heart rhythm dysregulation, and autonomic imbalance characterized by increased sympathetic and decreased parasympathetic drive to the heart. In Experiment 2, behaviors related to depression and endocrine function were measured following social bonding and social isolation in both male and female prairie voles. Social isolation produced similar levels of depressive behaviors in both sexes, as well as significant elevations of adrenocorticotropic hormone and corticosterone. These alterations in behavioral and physiological functioning provide insight into the mechanisms by which social stressors negatively influence emotional and cardiovascular health in humans.

1. Introduction

Supportive social relationships have a positive influence on mood and emotion as well as physiological functioning. For instance, they help protect against cardiovascular disease (CVD), improve responses to depression, and facilitate adaptive stress coping reactions (Blazer, 1982; Orth-Gomér et al., 1993; Frasure-Smith et al., 2000; Kikusui et al., 2006; Cacioppo and Cacioppo, 2012; Eisenberger, 2013; Norman et al., 2013). Frasure-Smith et al. (2000) assessed baseline depression and social support in patients suffering from myocardial infarction, along with cardiac prognosis and changes in depression symptoms after the infarction. High levels of perceived social support were associated with improvements in depressive symptoms and a reduced impact of depression on mortality over the first year following the infarction.

Conversely, disruption of social bonds, social isolation, and perceived isolation (loneliness) are associated with various forms of dysfunction and mortality both in humans and animal models (Seeman and Crimmins, 2001; Cacioppo and Hawkley, 2003; Uchino, 2006; Grippo et al., 2007c, 2011; Barger, 2013). For example, individuals with low levels of social engagement experience an increased risk of general and CVD-related mortality (Ramsay et al., 2008); and both social isolation and feelings of loneliness are correlated with increased mortality in older men and women (Steptoe et al., 2013). Men and women may respond differently to social and environmental stress. While some studies indicate that women are more likely than men to experience depressive or anxiety disorders, men are more likely to report greater impairment in everyday functioning as a result of these psychological disturbances (Scott, 2011).

The specific neurobiological mechanisms that underlie emotional and cardiovascular dysfunction are not well defined, however, both types of disorders share similar physiological dysfunctions and both appear to be influenced by the social environment. A better understanding of the influence of social experiences on health may lead to improved outcomes for millions of individuals worldwide affected by CVD and/or depressive disorders (Murray and Lopez, 1996; National Institute of Mental Health, 2009; American Heart Association, 2011). Both depression and CVD are characterized by an imbalance of autonomic cardiac regulation, altered heart rate (HR) and heart rate variability (HRV), vascular disturbances, and neurohumoral and immune dysregulation (Hance et al., 1996; Penninx et al., 2001; Carney and Freedland, 2003; Dantzer, 2006; Burg et al., 2013). Similarly, endocrine dysregulation (such as increased cortisol) is linked with atherosclerosis

* Corresponding author at: Department of Psychology, Northern Illinois University, PM 357, DeKalb, IL 60115, United States. Tel.: +1 815 753 7070; fax: +1 815 753 7088.
E-mail address: angelagrippo@niu.edu (A.J. Grippo).

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of carotid arteries (Dekker et al., 2008), and hypothalamic–pituitary–adrenal (HPA) axis dysfunction has been implicated in depression (Holsboer et al., 1984; Hinkelmann et al., 2009). These endocrine and autonomic mechanisms may be disrupted during social stress, which are likely to influence stress reactivity in both depressive and cardiovascular disorders. Social support has been suggested to have a positive influence on health by increasing an individual's valuation of self-esteem, control, and health behaviors; and decrease his/her appraisal of stress (Uchino et al., 1999). This down-regulation of responses to adverse events may in turn decrease the stress placed on the individual's body, resulting in more adaptive responses to stressors and greater overall health (Uchino et al., 1999).

Studies involving animal models provide insight into the neurobiological and biobehavioral mechanisms that underlie the associations among social stress, emotion, and cardiovascular dysfunction. In particular, the prairie vole is a socially monogamous rodent species that provides an excellent tool for studying relationships among the social environment, behavior, and physiology. These rodents form monogamous social bonds between males and females, live in extended families, and engage in biparental and allo-parental care of offspring, similar to human social systems (Getz et al., 1981; Carter, 2001; Cushing et al., 2001; Young and Wang, 2004). Prairie voles have been employed previously to investigate the neurobiological basis of attachment behavior (DeVries et al., 1995; Aragona et al., 2003; Cushing et al., 2003) and several aspects of dysfunction as a result of isolation and the disruption of social bonds (Grippo et al., 2007a; Bosch et al., 2009; Pournajafi-Nazarloo et al., 2011; Grippo et al., 2012; Lieberwith et al., 2012).

Substantial evidence indicates that prairie voles are sensitive to disruptions of the social environment. For example, female prairie voles exposed to long-term social isolation from a family member exhibit several deleterious changes in behavioral, endocrine, and autonomic function including depressive and anxiety behaviors, increased HR, decreased HRV, exaggerated cardiac and neuroendocrine reactivity to acute stressors, dysregulated autonomic cardiac control, and endothelial dysfunction (Stowe et al., 2005; Bales et al., 2006; Grippo et al., 2007c, 2012; Peuler et al., 2012). Further, early life social isolation has been associated with anxiogenic behaviors and altered social interactions, in addition to increased expression of stress hormones in the paraventricular nucleus of the hypothalamus (Pan et al., 2009). Finally, male prairie voles exposed to short-term isolation from a female social partner exhibit poor stress-coping behaviors and increased circulating hormone levels following separation (Bosch et al., 2009). These characteristics contribute to the utility of the prairie vole for the investigation of neurobiological mechanisms underlying social stress and negative health consequences.

The specific autonomic and endocrine mechanisms underlying the effects of disrupted pair bonds are not well understood. As such, the study of disrupting male–female social bonds in prairie voles, such as that described by Bosch et al. (2009), offers a unique opportunity to investigate the neurobiological mechanisms that may influence physiological and psychological dysfunction following partner loss. The present experiments investigated the disruption of an established social bond between male and female prairie voles. Experiment 1 investigated the specific effects of social bond disruption on depressive behaviors, and autonomic and cardiac function in male prairie voles. Experiment 2 extended the investigation of the deleterious effects of disrupted social bonds on behavior and neuroendocrine function in both male and female prairie voles. These experiments tested the hypothesis that the disruption of established social bonds would result in: (a) adverse changes in autonomic and cardiac regulation during basal and stress periods, including increased HR, decreased HRV, and autonomic imbalance; (b) increased neuroendocrine reactivity following exposure to stress; and (c) behavioral responses to stress that are associated with negative affective states. The investigation of these changes in a translational animal model will help explain the underlying mechanisms by which social stressors deleteriously influence behavior and physiology in humans.

2. Methods and materials

2.1. Experiment 1

2.1.1. Animals

Seventeen male prairie voles (60–90 days old) were bred in-house at Northern Illinois University. Offspring were removed from breeding pairs at 21 days of age, and housed in same-sex sibling pairs until the commencement of experimentation. Animals were allowed ad libitum access to food and tap water, maintained at a room temperature of 20–21 °C and a relative humidity of 40–50%, and under a standard 14:10 light/dark cycle (lights on at 0630). All experimental protocols were approved by the Northern Illinois University Institutional Animal Care and Use Committee and followed National Institute of Health guidelines as stated in the *Guide for the Care and Use of Laboratory Animals*.

2.1.2. General experimental design

Table 1 depicts the timeline of all procedures in Experiment 1. Briefly, a radiotelemetry transmitter was implanted into each male prairie vole for the recording of continuous electrocardiogram (ECG) and activity variables. Following recovery, animals underwent a baseline period of ECG and activity recordings. Each experimental animal was then removed from its home cage and paired with an unrelated female prairie vole. A social bonding assessment was conducted during this period to determine whether the prairie vole pairs had formed a bond. Five days after pairing, half of the pairs were housed individually ($n = 9$), while the other half remained as pair-housed controls ($n = 8$) for an additional 5 days. A forced swim test (FST) and assessments of autonomic nervous system function were conducted following the social isolation/pairing period (while the experimental group remained isolated). Handling and cage changes were matched between the groups.

2.1.3. Telemetric transmitter implantation

Wireless radiofrequency transmitters (model TA10ETA-F10; Data Sciences International, St. Paul, Minnesota) were implanted intraperitoneally into male prairie voles similar to methods used previously (Grippo et al., 2007b). Animals were anesthetized with a mixture of isoflurane (Baxter, IL USA) and oxygen throughout the surgical procedures. Briefly, the body of the transmitter was implanted into the intraperitoneal space, and wire leads were sutured (subcutaneously) to the muscle on the left and right of the heart. Following transmitter implantation, animals were housed for 5 days in custom designed divided cages that permitted adequate healing of suture wounds (see Grippo et al., 2007b). All animals were then returned to standard cages (with the

Table 1
Experimental timeline for Experiment 1.

Procedure	Schedule
Telemetric transmitter implantation	Days 1–2
Recovery in divided cages	Days 2–6 (depending on date
- ECG and activity measurements	of transmitter implantation)
Recovery in standard cages	Days 6–12 (depending on date
- ECG and activity measurements	of transmitter implantation)
Baseline period	Days 12–15
- ECG and activity measurements	
5 day social bonding period	Days 15–20
- ECG and activity measurements	
Social bond assessment	Day 17
- Digital video recording of behavior	
5 day isolation period	Days 20–25
- ECG and activity measurements	
Forced swim test	Days 25–26
- With continued isolation	
- Digital video recording of behavior	
- ECG and activity measurements	
Assessment of autonomic nervous system function	Days 28–34
- With continued isolation	
- ECG and activity measurements	