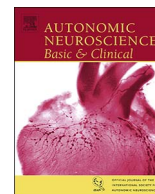




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## Cardiovascular control is associated with pair-bond success in male prairie voles

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## ABSTRACT

Social support structures reduce mortality and morbidity in humans, but the mechanisms underlying these reductions are not fully understood. The prevailing hypothesis is that social support buffers stress and reduces allostatic load, thereby increasing longevity. However, the possibility that affiliative social interactions confer health benefits independent of stress buffering is understudied. We examined autonomic function in prairie voles - arguably the premier species for modeling human social affiliation - to assess the possibility that the formation of strong social bonds alters autonomic function and contributes to health benefits. We examined cardiovascular measures in male prairie voles before and after two weeks of cohabitation with a female, during a partner preference test, and during social isolation. There were strong correlations between social contact and heart rate (HR) and heart rate variability (HRV), the latter being an index of autonomic nervous system function. Males that successfully pair-bonded with their partners displayed higher HRV prior to pairing than did unsuccessful males, suggesting higher basal parasympathetic tone in the successful males. HRV increased further still when pair-bonded males huddled quietly with their mates during the partner preference test. Non-pair-bonded males not only had lower baseline parasympathetic activity, but showed a further decrease after pairing. HR increased and HRV decreased during social isolation only in pair-bonded males. Since differences in HRV are thought to reflect the relative influences of the parasympathetic and sympathetic nervous systems on cardiac function, these results suggest that autonomic balance may contribute to social bonding and thus to its health benefits.

## 1. Introduction

Social connections reduce mortality and morbidity risk in both humans (Holt-Lunstad et al., 2010; House et al., 1988) and lower animals (Barocas et al., 2011; Silk et al., 2003; Yee et al., 2008) but the mechanisms by which these reductions are mediated are not well understood. Socially integrated people engage in more health promoting behaviors (e.g., increased compliance with medical regimens) and also display attenuated reactivity to stressors (Phillips et al., 2009; Umberson, 1992). However, other effects of affiliative social relationships, such as positive emotional states, have been understudied. This omission is puzzling, as previous research has shown that positive emotional states correlate with longevity (Burns et al., 2008; Kok et al., 2013; Reblin and Uchino, 2008), and that emotional state is regulated, in part, by the social environment (Heerdink et al., 2013; Kappas, 2013; Shuman, 2013). Thus, social modulation of the physiological correlates of positive emotional states may promote increased longevity in socially integrated persons.

Autonomic functioning appears to play a role in mediating the

experience of different emotional states (Kreibig, 2010; Stemmler et al., 2007). According to the James-Lange theory of emotions, behavioral and physiological reactions to motivationally-relevant stimuli in the environment stimulate visceral sensory afferents, creating the emotional experience (Friedman, 2010). While autonomic specificity of discrete autonomic states is controversial (Barrett, 2006; Kreibig, 2010), it is generally accepted that autonomic responses are related to the valence (i.e., positivity or negativity) of an emotional state (Cacioppo et al., 2000). This has led to the suggestion that the health-benefits of social affiliations are mediated by patterns of autonomic functioning associated with positive emotional states engendered by affiliative social relationships.

Animal research has provided support for the relationship between autonomic physiology and emotional states (Buwalda et al., 1999; Nakata et al., 1993; Salome et al., 2007; Sgoifo et al., 1999) including in social contexts (Sgoifo et al., 2014). Of note, lower animals express changes in autonomic function consistent with those experienced by humans in analogous circumstances (Donoho et al., 2015; Porges, 1998). For example, acute stressors (Shively et al., 2007) and the

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emotional valence of videos (Bliss-Moreau et al., 2013) elicit autonomic responses in non-human primates that mirror observations made in human studies (Mendes, 2009). In rodents, social defeat leads to elevated heart rate (HR) (Costoli et al., 2004; Nalivaiko et al., 2009) and reduced heart rate variability (HRV) (Costoli et al., 2004). However, those effects can be mitigated when the defeated animal is returned to its familiar group (Bradley, 1999). Sexually naïve prairie voles (*Microtus ochrogaster*) show increased HR and decreased HRV in response to chronic social isolation (Grippo et al., 2007, 2012). Similarly, mated prairie voles show elevated HR and reduced HRV when separated from their partners (McNeal et al., 2014). Altered autonomic responses also have been observed during pup exposure, presumably a positive emotional experience, in both sexually naïve (Kenkel et al., 2013) and paternal (Kenkel et al., 2014) male prairie voles. Thus, support for the role of the social environment in regulating autonomic responses to emotionally valent stimuli has been observed in a variety of animal models.

Among animal models, prairie voles have a significant advantage over more traditional laboratory rodents as an animal model in which to study autonomic physiology in social contexts. Prairie vole social behavior is well-characterized and closely resembles that of humans (Carter and Getz, 1993). Both sexes typically form monogamous pair-bonds with their mates and contribute to parental care, and pairs occupy the same nest even beyond the breeding season (Carter and Getz, 1993; Carter et al., 1986; Getz and Hofmann, 1986). Sexually naïve prairie voles are highly social and avoid isolation to the point that they appear to actively seek out contact with other voles (Shapiro and Dewsbury, 1990). However, after forming a pair-bond with a mate, a remarkable transformation occurs: these previously very social animals begin to display strong aversions to contact with strangers. Rather than seeking out companions, they actively avoid contact with, or display aggression toward, strangers (Aragona et al., 2006; Insel et al., 1995). Instead, they appear to be highly motivated to engage in close affiliation with their respective familiar partners. Thus, pair-bonding induces patterns of motivated behavior that are characterized by approach responses directed toward the partner and avoidance/defensive behaviors directed toward strangers. According to the James-Lange theory of emotion, these patterns of motivated behavior are associated with different autonomic responses and reflect distinct underlying emotional states.

Although all prairie voles appear to be capable of forming pair bonds, a given pair may not be reproductively compatible. Female prairie voles do not display a spontaneous estrous and do not mate, or may be delayed in mating, unless paired with a compatible male (Curtis, 2010b). The importance of timely and successful mating for social behaviors is illustrated by responses of males to their partners or to strangers, which differ depending on whether or not the male and his partner successfully mated within 2–3 days after pairing. For example, male prairie voles did not express affiliative behaviors associated with pair-bonding if their mates were not pregnant or showed evidence of delayed mating (smaller pups in utero) after two weeks of cohabitation (Curtis, 2010a). Similarly, Resendez et al. (2012) found that males from pairs with smaller pups in utero after two weeks of pairing did not display the stranger-directed aggression typical of pair-bonded males. Thus, delayed mating likely interferes with consolidation of pair bonds (Curtis, 2010a). Further, there is evidence that the differences in affiliative/avoidance behaviors may reflect differences in the expression of dopamine receptors in brain regions involved in motivated behavior (Aragona et al., 2006). At present, however, it is unknown whether patterns of autonomic functioning associated with social relationships in voles may be affected by the formation of pair-bonds.

The purpose of the present study was to test the hypothesis that pair-bonding alters autonomic responses to the familiar partner as well as to strangers. We took advantage of the natural variation in mating success and pair-bond formation noted above to examine autonomic function in pair-bonded and non-pair-bonded voles during a social choice test. We also compared autonomic activity in the absence of a

familiar animal in pair-bonded and non-pair-bonded voles. If pair-bonded prairie voles respond differently to the presence or absence of the partner in ways that differ from those displayed by non-pair-bonded voles, then the “emotional” response to the partner may change after forming a pair-bond.

## 2. Materials and methods

Subjects were sexually-naïve adult male prairie voles from a captive breeding-colony at Oklahoma State University's Center for Health Sciences, and were of the F3 and F4 generations relative to the most recent outcrossing with wild stock. Voles were weaned at  $20 \pm 0.5$  days of age, after which they were housed as same-sex pairs in shoebox style Plexiglas cages ( $10 \times 17 \times 28$  cm) with *ad libitum* access to food (Purina rabbit chow supplemented with black oil sunflower seeds) and water. Photoperiod (14:10 light/dark cycle) and temperature (about 21 °C) were maintained throughout the year. The average age of the voles at the beginning of the experiment was  $117.4 \pm 30.5$  days of age, and the average mass was  $43.9 \pm 3.2$  g and there were no significant age or mass differences among the animals used in the experiments. All surgical and behavioral procedures were approved by the Oklahoma State University Center for Health Sciences Institutional Animal Care and Use Committee.

### 2.1. Overview of experimental timeline

Radiotelemetry devices for monitoring activity and blood pressure (BP) were surgically implanted in males and they were allowed 7 days to recover (Lewis and Curtis, 2016) after which a 24 h pre-pairing (Baseline) recording of each male's blood pressure was obtained. On day 10 after surgery, each male was paired with a randomly selected and unrelated sexually naïve female. On day 13 after pairing (day 23 after surgery), a second 24 h recording was obtained from each animal. On day 14 after pairing (day 24 after surgery), males were subjected to a 3-h choice-test with the choices being affiliation with the familiar female with which that they had cohabited for two weeks, or with an unfamiliar female stranger. Telemetry data were collected from each male throughout the duration of the partner preference test. Following the preference test, the female mates were sacrificed and the status of their pregnancies was assessed. Activity and blood pressure then were recorded from the socially isolated males for an additional 24 h.

### 2.2. Surgery and telemetry data recording

Pressure-sensitive radiotelemetry devices (PA-C10, Data Sciences International) were implanted as previously described (Lewis and Curtis, 2016). Briefly, the catheter tip was inserted into the left common carotid artery and advanced 14–14.5 mm from the carotid bifurcation into the aortic arch. The body of the device was placed in a subcutaneous pouch over the animal's right scapula. Animals that lost more than a few drops of blood were given a subcutaneous injection of isotonic saline (~0.5 mL). On the day of surgery, animals were given 0.1 mL of meloxicam (1.5 mg/mL) orally for post-operative pain management. During data recording, cages were placed on receiver plates (Data Sciences International) designed to receive input from the telemetry device. Dataquest ART software was used to acquire activity and BP measurements. Activity and BP were sampled at 500 Hz. Measurements for each parameter were generated in 10 s epochs. An ambient pressure monitor (APR-1, Data Sciences International) was used to correct for atmospheric pressure.

### 2.3. Baseline recording and pairing

Following surgery, each instrumented male was re-united with its same-sex cage-mate; however, they were separated by a wire mesh barrier which permitted visual, auditory and olfactory contact, but

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