ORIGINAL RESEARCH

Massage Increases Oxytocin and Reduces Adrenocorticotropin Hormone in Humans

Vera Morhenn, MD; Laura E. Beavin, MA; Paul J. Zak, PhD

ABSTRACT

Context • Human beings are highly social creatures who often touch each other during social interactions. Although the physiologic effects of touch are not understood fully, it appears to sustain social bonds and to increase cooperative behaviors. Oxytocin (OT) is a hormone known to facilitate social bonding, and touch may affect OT release. Previous studies seeking to relate massage and oxytocin in humans have been inconsistent in their findings.

Objectives • This study examined the effect of massage on oxytocin and also measured its effect on other physiologic factors, including adrenocorticotropin hormone (ACTH), nitric oxide (NO), and beta-endorphin (BE).

Design • The research team advertised that the trial would study relaxation and assigned participants randomly to the intervention or the control group. A lab administrator assigned a random numeric code to participants to mask their identities.

Setting • The study took place at the University of California Los Angeles (UCLA), Los Angeles, CA.

Participants • Ninety-five people from UCLA gave written informed consent for participation in the study, with the team paying them to participate. The intervention group included 65 participants and the control group 30 participants.

Intervention • For the intervention (massage) group, the research team drew participants' blood and followed the blood draw with 15 minutes of moderate-pressure massage of the upper back. The control (rest) group rested quietly for 15 minutes after the blood draw. A second blood draw followed for both groups.

Outcome Measures • The research team assayed OT, ACTH, NO, and BE. The team used four survey instruments to examine the relationship between personality factors and the physiologic measures of interest. The team analyzed data using SPSS 15.0 for Windows.

Results • Massage was associated with an increase in OT and reductions in ACTH, NO, and BE. Comparing the effects of massage for the massage group with those for the rest group, the research team found significant differences between groups for changes in OT, ACTH, NO, and BE .

Conclusions • This study is the first using a large sample of mixed gender that demonstrates that massage increases OT and decreases ACTH, NO, and BE. These findings may help explain the mechanisms through which social connections reduce morbidity and mortality. (*Altern Ther Health Med.* 2012;18(6):11-18.)

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It is not unusual for human beings who meet for the first time to touch each other. Most people who know each other nearly always touch upon meeting (eg, with handshakes, hugs, or kisses). Physical contact of various sorts during encounters is also common among animals. Nonhuman primates spend a substantial amount of time touching and grooming to sustain social bonds, decrease stress, and reconcile after aggression.[1-3] Although the physiologic effects of touch are not fully understood, touch in humans appears to sustain social bonds[4] and to increase cooperative behaviors.[5]

At the same time, a lack of research has allowed few robust conclusions regarding the physiologic mechanisms behind the finding that active social networks seem to reduce morbidity and mortality.[6] People with more extensive social networks have fewer hospital readmissions and health-care visits, and also spend less on health care.[7,8] Larger social networks and frequent contact with friends also has been associated with a lower instance of depression.[9] Conversely, for

those individuals with limited social networks, women have higher rates of psychiatric disorders while older males and females have a 60% increase in risk of dementia.[10,11] The life expectancy for seniors with small social networks is shorter than for those who regularly participate in social activities.[12-14]

Some researchers have linked the improved health outcomes for individuals with larger social networks to neuroendocrine changes as well as improvements in immune function. For example, social networks may protect health by buffering stress; chronic stress can suppress immune function.[15,16] In part, the physiology of touch might explain why social networks reduce morbidity and mortality. In patients with hypertension, massage therapy decreased blood pressure and depression.[17,18] Massage also appears to decrease cortisol and increase dopamine and norepinephrine levels.[4,19,20] In addition, Ironson et al have provided evidence that massage boosts the immune system in AIDS patients, increasing the number of natural killer cells as well as their activity.[21]

The current research examined the effect of touch on oxytocin (OT) release and associated physiologic factors that are part of the neural architecture of appropriate social behaviors.[22] The research team's previous research showed that an intentional signal of trust, measured by a monetary transfer from one person to another, induced OT release in proportion to the amount of money received.[23] Preceding the monetary transfer with a 15-minute, moderate-pressure back massage increased the OT levels and the amount of reciprocity after receiving money denoting trust.[5]

In the current study, the research team examined whether massage alone would stimulate OT release. The team also measured the associated effects on adrenocorticotropin hormone (ACTH), nitric oxide (NO), and β-endorphin (BE), all of which are markers that interact with OT or that massage affects, according to previous research.

OT was the team's primary target because it acts as an anxiolytic and promotes social intercourse.[23,24] Several studies have shown that OT, measured in peripheral blood, increases when one is trusted and when one feels empathy.[23,25,26] Studies that have infused OT into humans have shown that it increases trust, generosity, and eye gaze towards others.[27-29] Trust, generosity, and empathy are important in sustaining social relationships.[22]

Some research has shown that stroking animals can induce OT release.[30,31] Unfortunately, the relationship between touch and OT release in humans is unreliable. Two small studies found no increase in OT after massage.[32,33] Relatedly, 10 minutes of hugging by a person's partner did not produce an acute effect on OT levels,[34,35] and a shoulder-and-neck massage by a partner did not elicit an OT change in women enduring a stressor.[36] A study examining married couples found that compared to a control group, a 4-week intervention involving 30 minutes of warm touch and massage three times a week was associated with higher levels of salivary but not plasma OT for both males and females.[37] On the other hand, a study comparing deep-pressure massage to light touch found that deep-pressure massage did not affect OT or ACTH, but that light touch led to a 27% increase in OT and a 24% decrease in ACTH in 24 participants.[38] The research team's previous work[5] showed only a trend relating massage and OT for a small number of participants (N = 24). That study found that massage alone did not raise OT; rather, monetary transfers denoting trust produced an increase in OT. When the receipt of a monetary transfer denoting trust was coupled with massage, OT increased by 16% above the increase from trust alone.

The current trial sought to test whether massage alone would raise OT when studying a larger sample of volunteers. The research team hypothesized that 15 minutes of massage would raise OT, while rest alone would not change, or might even decrease, OT. The team also predicted that massage would decrease hypothalamic-pituitary-adrenal (HPA) axis activity, as several studies have found.[39] Studies have shown that elevated stress responses[40,41] and social isolation[42,43] are associated with cardiovascular disease and increased morbidity and mortality. Although elevated cortisol is associated with stress, cortisol does not begin to rise until about 10 minutes after stimulation and ACTH release precedes it.[44] Because of the 15-minute massage stimulus that the current study used, the research team selected ACTH as a measure of stress.[45] The team hypothesized that massage would reduce ACTH.

The research team also assayed two additional physiological factors that may be involved in the response to massage. The team assayed BE because it is an endogenous opioid, and keratinocytes can produce it. Researchers have proposed that BE synthesis may be a mechanism by which massage reduces pain.[46] Furthermore, Foley et al have linked BE to the relaxation and feelings of well-being that accompany massage.[47] A study that investigated the impact of skin-to-skin touch between mothers and infants showed that BE decreased in infants after touch.[48] Previous tests of the relationship between BE and massage, however, have produced mixed results.[46,49] Studies also have linked BE to social-contact behaviors in animals, such as grooming.[50,51] In the current study, the research team predicted that BE would show a significant increase in participants who received massage. The team also assessed NO, an endothelium-derived relaxing factor, because keratinocytes produce and release it and because it causes smooth muscle relaxation.[52] NO release causes vasodilation and reduces cardiovascular tone.[53] Phagocytes also produce NO as part of the human immune response.[54] The research team predicted that massage would increase NO because of the vasodilatation and relaxation that typically follow massage.[55]

METHODS

Participants

The research team advertised that the trial would study relaxation. Ninety-six people from the University of California, Los Angeles (UCLA) gave written informed

consent for participation in the study, with the team paying them to participate. One participant in the massage group dropped out of the study after he became queasy during the first blood draw, leaving 95 in the final sample (mean age 21.36 years, SD = 3.46). A rest condition served as the control, and to ensure the validity of the treatment, the team assigned more participants to the intervention condition than to the control. The research team assigned participants randomly to the intervention (massage) group (N = 65) or the control (rest) group (N = 30).

The overall sample had 52.6% females, and about half of the participants in both groups were female (massage = 52.3%; rest = 53.3%). Each session of the experiment included 8 to 14 participants, to whom a lab administrator assigned a random numeric code to mask their identities. All sessions began at 10 AM to control for possible diurnal variations in physiologic measures and lasted about 1.5 hrs. The Institutional Review Boards at UCLA and Claremont Graduate University approved this study.

Materials and Procedure

To control the type of touch, the same three massage therapists massaged all participants in the intervention group. Participants in that group received 15 minutes of moderate-pressure Swedish massage on their upper backs while lying prone on a massage table with their clothes on and shirts lifted to their shoulders. Massage took place in a semiprivate room, and one of three female, licensed massage therapists provided it. The research team instructed the therapists to minimize conversation with the participants, and the same therapists assisted in every session. The team informed participants in advance that they had asked the massage therapists not to converse with them. The team asked participants in the control group to rest by sitting in chairs for 15 minutes in the same rooms where participants in the massage group had received massages. The massage and rest sessions were run during different days, and the therapists removed the massage tables during the rest sessions to ensure that the control group did not know that participants in the massage group had received massages.

Blood Draw

After participants signed the informed consent, the research team took them to a private room for their first blood draw. A licensed phlebotomist drew 20 mL of blood from an antecubital vein for all participants. The phlebotomist drew two 8-mL, EDTA (ethylenediaminetetraacetic acid) whole-blood tubes and one serum-separator tube while maintaining a sterile field and using a Vacutainer. Some of the participants in the massage group (N = 41) and all of the participants in the rest group (N = 30) participated in an economic task after the massage, as described in Morhenn et al (2008), and these participants had a second, 20-mL blood draw immediately following the completion of the task. Participants in the massage group who did not participate in the economic task (N = 24) received their second blood draw immediately following the 15 minutes of massage.

After the phlebotomist drew the blood, the research team placed each tube on ice. The research team then placed the tubes in a refrigerated, clinical centrifuge; chilled them to 4°C; and spun them at 1500 rpm for 12 minutes. The team withdrew plasma and sera from the tubes using disposable pipettes and placed them into 2-mL microtubes with screw caps. The team immediately placed these tubes on dry ice and then transferred them to a -80°C freezer for storage until the assays were performed.

OUTCOME MEASURES

Assays

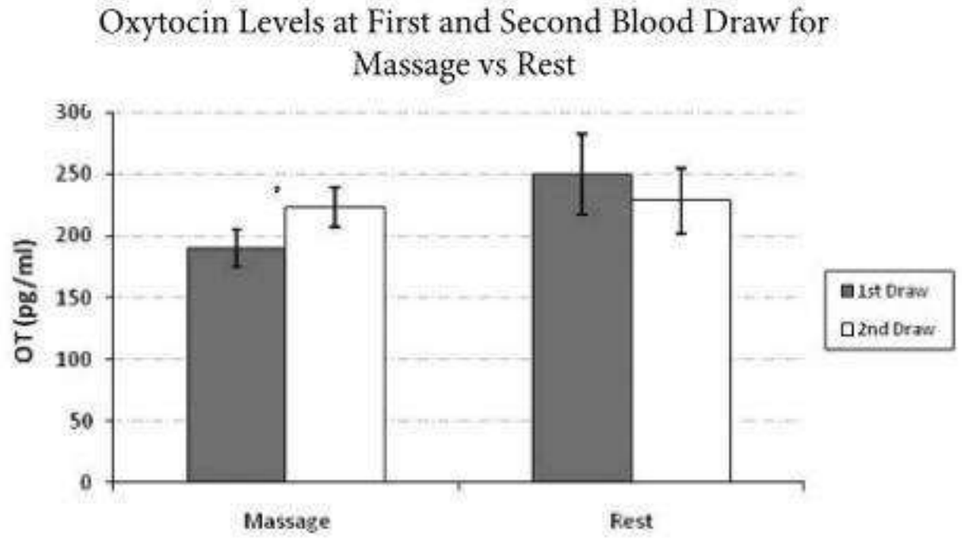
OT, ACTH, and NO assays were done at the Endocrine Core Laboratory of the Yerkes National Primate Research Center at Emory University (Atlanta, GA) using commercially available kits. The team assayed OT using a competitive EIA kit from Assay Designs (Ann Arbor, MI). The team did not perform an extraction step before the assay, based on consultations with Assay Designs and on several analyses by the Biomarkers Core at Emory University. The research team's lab and other labs have used unextracted samples in previous studies.[5,23,25,56] Unextracted OT is known to produce assay values for OT that are between 10 and 100 times higher than extracted values,[57] but the team's focus was on the change in OT; so this approach mitigated the effect. The inter- and intra-assay coefficients of variation were 7.48% at 484.68 pg/mL and 10.2% at 494.63 pg/mL (10 replicates), respectively.

The research team assayed ACTH using RIA kits from DiaSorin (Stillwater, MN). The inter- and intra-assay coefficients of variations for the first kit were 15.40% at 38.70 pg/mL and 8.63% at 16.03 pg/mL (10 replicates) and for the second kit were 9.83% at 111.87 pg/mL and 2.94% at 87.77 pg/mL (10 replicates). Since NO is a gas, the research team could document only its breakdown products in serum. As a result, the nitrites in the serum were assayed using an ELISA kit from Bioassay Systems (Hayward, CA) with a 4% coefficient of variation. Lastly, the research team assayed BE with an EIA kit from Bachem (Torrance, CA), showing a 13.36% interassay coefficient of variation (6 replicates).

Surveys

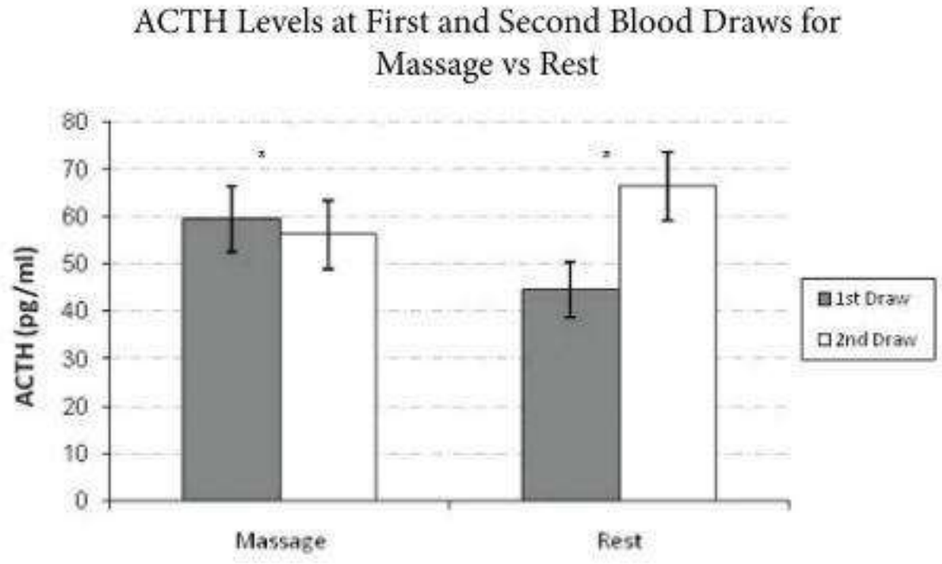
The research team used four survey instruments to examine the relationship between personality factors and the physiologic measures of interest. These surveys included (1) the Affective Intensity Measure (AIM) that assesses the intensity with which people feel emotions,[58] (2) the Self Monitoring Scale that measures the ability to control emotional expressiveness to appropriately fit a situation,[59] (3) the Experiences in Close Relationships-Revised (ECR-R) that measures attachment styles,[60] and (4) demographic and general attitude questions taken from Zak, Borja, Matzner, and Kurzban.[61] The team included the surveys to assess the role of personality traits on changes in OT and other physiologic measures, if any.

Figure 1. Oxytocin Levels at First and Second Blood Draw for Massage vs Rest



Comparison of average OT levels at baseline and at the second blood draw for participants who received massage and participants who rested, with SE bars. Massage was associated with a 17% rise in OT, which was a significant increase over basal levels ($P < .001$). The rest group had a 9% decrease in OT ($P = .094$). This difference shows that massage changes the release pattern of OT.

Figure 2. ACTH Levels at First and Second Blood Draws for Massage vs Rest



Basal and poststimulus, mean ACTH with SE bars for participants who received massage and who rested. ACTH decreased 6% for the massage group ($P < .01$), and increased 49% for the rest group ($P < .001$). As with OT, massage appears to have changed the release pattern of ACTH.

Statistical Analysis

The research team analyzed data using SPSS 15.0 for Windows (SPSS, Chicago, IL). A percentage of participants took part in an economic task called the trust game, as described in Morhenn et al, and this task involved a single monetary decision that studies have shown influences physiology.[5, 25] To remove the effect of the monetary decision, the research team ran a least-squares regression on each physiologic measure, using a variable coding for participation in the task and a variable representing the monetary transfer as the two predictors. The team then saved the residuals and added them to the mean of each measure so that a subsequent value of a measure removed the effect of the monetary-decision task. The team performed this transformation only on measures from the second blood draw for participants who received monetary transfers; no transfers preceded the first blood draw. The research team used a battery of tests that showed that the statistical procedure used to remove the effect of the decision task was successful. See the appendix for this procedure. The team used paired *t* tests for within-subjects comparisons when applicable and nonparametric tests when the conditions for a *t* test were not satisfied. All reported values for *t* tests are two-tailed, unless otherwise specified. The research team tested for between-subjects effects, with regressions controlling for basal levels of physiologic measures. The team also ran repeated-measures ANOVAs, and the findings were identical to paired *t* tests (Appendix).

RESULTS

Assays

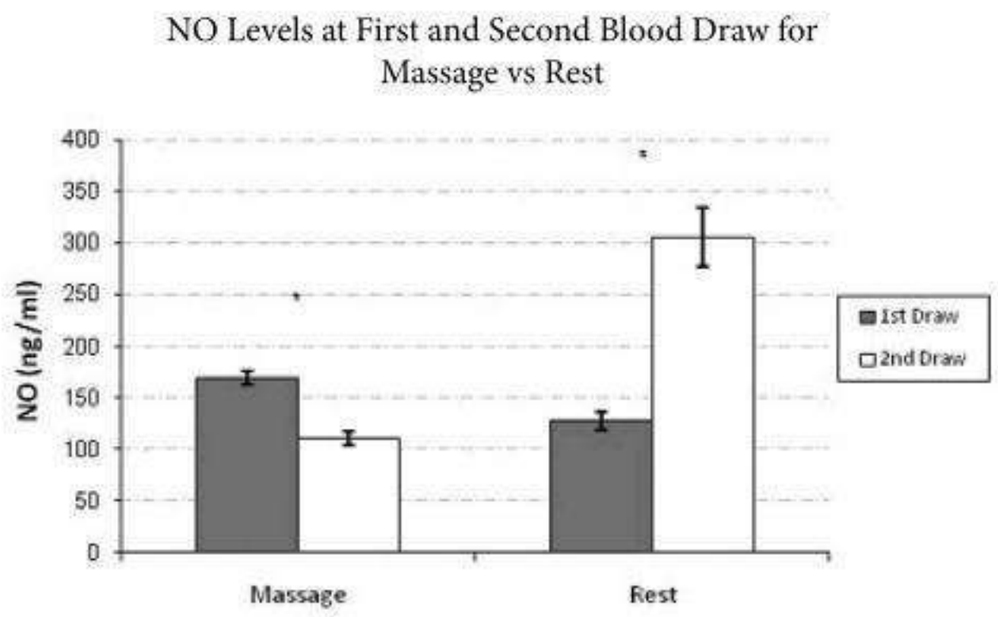
Basal OT is highly variable absent a stimulus for its release.[62] Before performing between-group comparisons, the research team ran an ordinary least-squares (OLS) regression to confirm that basal OT for participants in both groups was unrelated to treatment condition ($P = .393$). The team obtained the same result for basal values of the other physiologic measures (ACTH: $P = .780$; NO: $P = .975$; BE: $P = .848$). As a result, between-group comparisons are valid. In testing for differences between groups, the research team ran OLS regressions controlling for basal levels of each physiological measure and massage as a predictor of physiological measures at the second blood draw. The research team also used independent-samples *t* tests to determine whether a significant difference exists between groups for the change in physiological measures.

OT Assays. Consistent with the research team's primary hypothesis, the assays indicated that individuals receiving massages showed an increase in OT between baseline (M1 = 190.37 pg/mL, SD = 122.04) and the second blood draw (M2 = 223.50 pg/mL, SD = 127.16) producing a significant change ($P < .001$). A similar comparison in the control group showed a decrease in OT that trended toward significance (M1 = 249.93 pg/mL, SD = 173.51; M2 = 228.46 pg/mL, SD = 57.31; $P = .094$). See Figure 1.

Performing OLS regressions for the change in OT showed that massage was associated with higher OT compared to rest ($P < .001$) and that massage accounted for 2.8% of the variation in OT levels. A *t* test demonstrated that massage also accounted for the significant difference in the change in OT between the two groups (Massage: M = 33.13, SD = 28.78; Rest: M = -21.47, SD = 66.77; $P < .001$).

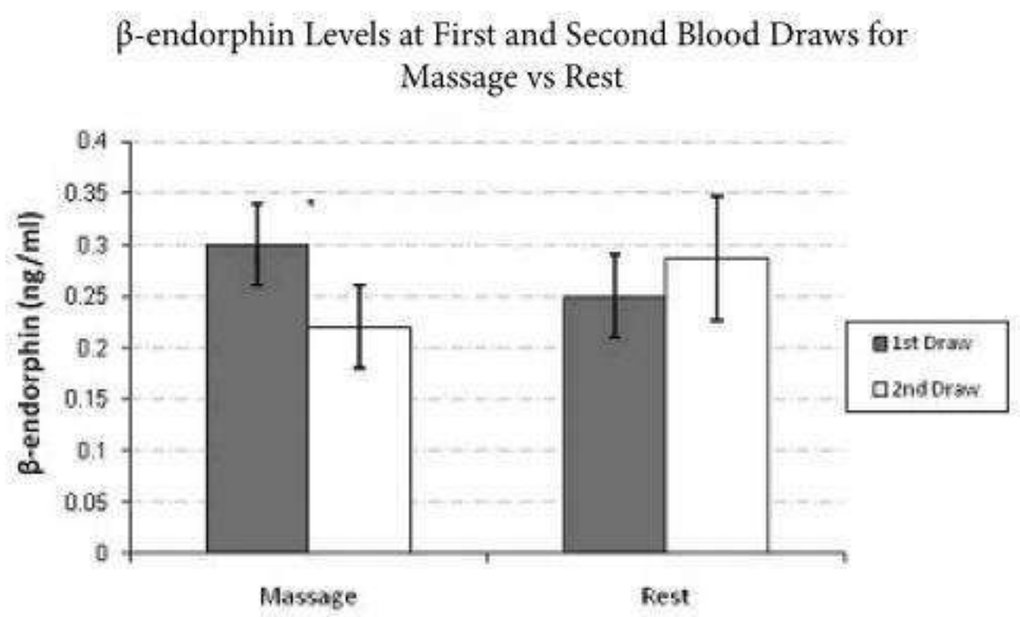
ACTH Assays. These assays found that ACTH decreased in those who received massage (M1 = 59.57 pg/mL, SD = 55.30; M2 = 56.14 pg/mL, SD = 57.31; $P = .012$). For participants who rested, levels of ACTH increased (M1 = 44.59 pg/mL:, SD = 30.78; M2 = 66.41 pg/mL, SD = 38.51; $P < .001$). See Figure 2.

Figure 3. NO Levels at First and Second Blood Draw for Massage vs Rest



Massage was associated with a 35% decrease in NO ($P < .001$). Those who rested showed a 140% increase ($P < .001$). As with OT and ACTH, this difference indicates that massage changes NO release.

Figure 4. β-endorphin Levels at First and Second Blood Draws for Massage vs Rest



Average level of BE before and after massage and rest. BE decreased 29% for those who received massage ($P < .01$), but did not change for participants who rested ($P = .185$).

Massage also was a significant predictor of lower ACTH levels for the rest vs the massage group ($P < .001$), with massage accounting for 5.1% of the variation in ACTH. The change in ACTH was significantly different in the two groups (Massage: M = -3.43, SD = 10.68; Rest: M = 21.82, SD = 13.67; $P < .001$).

NO Assays. Before examining the change in NO, the research team excluded one participant in the massage group because his basal NO was more than 4 SDs higher than the average. For the remaining data, massage decreased NO (M1 = 169.13 ng/mL, SD = 52.46; M2 = 110.45 ng/mL, SD = 54.52; $P < .001$). In contrast, those who rested had a significant increase in NO (M1 = 127.57 ng/mL, SD = 45.74; M2 = 305.51 ng/mL, SD = 150.70; $P = .001$). See Figure 3.

Massage predicted the difference in NO for the second blood draw, after controlling for baseline levels ($P < .001$), with massage explaining 39.5% of the variation in the levels of NO. Due to massage, the change in NO varied significantly between the two groups (Massage: M = -1.95, SD = 2.29; Rest: M = 5.93, SD = 5.64; $P < .001$).

BE Assays. Lastly, the team found that BE decreased in those who received massages (M1 = .30 ng/mL, SD = .27; M2 = .22 ng/mL, SD = .22; $P = .004$). No significant changes in BE occurred for participants who rested ($P = .185$). See Figure 4. Table 1 summarizes these findings.

BE repeated the pattern between groups. Those who received massaged showed a negative change in BE, while rest was associated with a positive change in BE (Massage: M = -.09, SD = .14; Rest: M = .04, SD = .16; $P < .01$). Massage accounted for 5.5% of the variation in the levels of BE at the second blood draw after controlling for baseline BE.

Correlations Between Assays. To understand more fully the physiologic effects of massage, the research team examined correlations between physiologic measures. For the group receiving massage, there was a significant negative correlation between the change in OT and the change in ACTH ($r = -.21$, one tailed t test $P = .05$). No other correlations between physiologic measures were significant for those who were massaged. Rest, on the other hand, was associated with a positive correlation between the change in BE and the change in OT ($r = .50$, $P < .01$). Additionally, there was a positive correlation between the change in ACTH and the change in NO ($r = .40$, $P = .034$) in the rest group.

Typically, women release more OT than men for all non-reproductive stimuli that have been studied to date.[22, 63] As a result, the research team examined whether gender affected the results using least-squares regressions. Women who received massage did not release significantly more OT than men ($P = .45$); however, women who rested did show a change marginally higher in magnitude than men (females' mean change in OT -49.71 pg/mL; males' mean change in OT, 8.78 pg/mL; $P = .056$). Massage alone predicted 25% of

Table 1. Percent Change in Physiologic Measures from Baseline to Second Blood Draw (N = 95)

	Massage	Rest
OT	+9%[a]	-18%[a]
ACTH	-20%[a]	+30%[a]
NO	-36%[a]	+91%[a]
BE	-30%[a]	ns

Abbreviations. OT, oxytocin; ACTH, adrenocorticotropin hormone; NO, nitric oxide; BE, beta endorphin.

[a]$P < .001$

the variation in OT change ($P = .017$), and massage and gender explained 30% of the variation in the change. Gender was not a significant predictor of change in ACTH ($P = .28$). Women also released more NO than men ($P = .023$). Gender was not associated with the change in BE ($P = .81$).

Surveys

Next, the research team used OLS regressions to examine whether personality traits affected the results through their interaction with physiological measures. The team first tested whether self-monitoring tendencies, as measured by the Self-Monitoring Scale, had an effect on the relationship between the experimental manipulation (massage) and physiological changes. The team found that scores on this scale did not interact with whether or not one received a massage for any of the physiological changes.

Next, the research team tested whether attachment style, as measured by the ECR-R, affected physiological changes. The research team found that those who were massaged and had stronger attachments released more OT ($P = .018$). The team did not find a relationship between attachment style and physiologic measures for those participants who rested.

As a final personality measure, the research team tested whether affective intensity, as measured by the AIM, impacted the observed relationships. The team found no effects for those participants in the massage or the control group.

Following earlier work relating oxytocin to trust,[23,25,27] the research team examined how the predilection to trust interacted with massage. The team performed this study by creating a composite score from responses to six attitude questions about trust. This measure significantly interacted with the experimental manipulation for the change in OT ($P = .005$), but not for other physiologic measures.

DISCUSSION

The research team began this investigation searching for a physiologic mechanism through which one aspect of social interactions, touch, might explain its positive health benefits. Both OT and ACTH were primary candidates. Using a large sample of mixed gender, the research team showed that 15 minutes of skin-to-skin, moderate-pressure back massage resulted in a 17% increase in OT within subjects. This change in OT is consistent with the findings of other studies that used other stimuli to induce OT release and that showed that OT release produced behavioral effects.[35,57] Massage may promote prosocial behaviors such as trustworthiness, generosity, and empathy.[23,25,26,28] Such prosocial behaviors help sustain social relationships. Although a previous study by Holt-Lunstad et al found that warm touch was associated with higher salivary OT than levels for a control group, this study did not find increases in plasma levels compared to baseline.[37] Furthermore, the researchers conducted the study with married couples who were trained to touch each other, and therefore does not reflect the effects for those individuals who receive treatment from massage therapists. Rappaport et al also found an increase in OT but only for participants receiving light touch, not for those who received massage.[38]

In the current study, massage produced a 6% decrease in the stress marker ACTH. By acting on corticotropin-releasing factor (CRF), OT inhibits ACTH release.[64-67] Indeed, the research team demonstrated a negative correlation between the increase in OT and the decrease in ACTH. This finding is a likely candidate to explain why social ties reduce morbidity and mortality; interacting with friends inevitably involves touching that reduces a marker for cardiovascular tone.

Contrary to expectations, the research team found that levels of BE decreased in participants who received a massage. Previously, researchers have suggested that BE is the potential mechanism by which massage reduces pain. One study found that massage increased BE,[49] while another found no change.[48] The results from the current study are difficult to interpret, as the participants were not in pain before receiving massage. The team's results are thus unable to clarify the relationship between BE and massage.

Clearly, a complex set of interactions occurs between the substances measured, but OT release is likely the initiator of this cascade of effects as it is released within seconds of a stimulus.[68, 69] Release times for the other substances measured are (1) 5 to 8 seconds for NO,[70,71] (2) 15 seconds for ACTH,[72] and (3) approximately 1 to 2 minutes for BE (in response to nonpainful stimuli).[73] The 35% decrease in NO after massage may have contributed to the increase in OT levels. NO regulates OT release, with the stimulation of nitric oxide synthase (NOS) inhibiting OT release.[74]

Several limitations to this study exist that other researchers should take into account when interpreting the results. First, massage accounted for only a small proportion of the variation in OT, ACTH, and BE, although it did account for a large proportion of the variation in NO. These findings may not be surprising given the substantial variation in most physiologic measures and the many effects of hormones on the body. Second, the assay procedure for OT did not include an extraction step, producing larger values and standard errors than would be found in an extracted sample. The research team's finding of a significant change in OT after massage without extraction was thus less likely, and yet, the study found it nonetheless.

Next, although OT is an anxiolytic, it is also released in response to moderate stress and may signify discomfort. The use of blood draws may have induced stress for participants. Participants were aware initially that the experiment involved blood draws, and the research team encouraged them to withdraw if they were uncomfortable with any part of the experiment. If the stress of the blood draws were driving the results, the control group would have had an increase in OT as well; instead their OT fell, indicating that stress is unlikely to be a concern.

Lastly, the participants in this experiment did not know the massage therapists who were touching them. During debriefing, not a single participant said they felt uncomfortable during the massage. Yet, the touch that occurs during a massage is different than that which occurs during typical

social interactions. As a result, the results of this study may not generalize to casual social interactions that do not involve such a high degree of touch, but rather, occur over extended periods of time. The research team did not expect that a brief massage, such as that employed in this study, would have the lasting physiological effects that close relationships can offer.

CONCLUSION

As researchers continue to discover the stimuli that increase OT,[22] they are beginning to document this peptide's positive health effects. These effects include (1) OT's ability to activate the adaptive immune system,[76] (2) its role as a stress buffer,[24,77] and (3) its potential ability to mediate depression.[75-79] Being trusted is another nonreproductive stimulus that induces OT release.[23,25] Trust and touch are an essential part of sustaining social ties. The mediating effects of OT on stress and possibly the immune system that this article reports provides evidence for the mechanism through which social relationships protect health.

Appendix A

A subset of the participants took part in a single-decision task involving money that has been shown to affect oxytocin (OT) (Zak, Kurzban & Matzner, 2005). Because the research team was interested solely in investigating the effect of massage on physiology, the team removed the effect of participating in the decision task and also the effect related to the amount of money participants sent or received during the task. To do this, the team ran a least-squares regression on each physiologic measure obtained from the second blood draw, with a variable coding for participation in the task and a variable representing monetary decision as the predictors. The team then saved the residuals and added them to the mean of each measure so that a subsequent value of a measure had the effect of the monetary-decision task removed. The team performed this transformation only on measures from the second blood draw for participants who received monetary transfers; no transfers preceded the first blood draw.

To test whether this method of removing effects was successful, the research team ran regressions on the transformed variables with the variables that the team had removed as predictors (Table A1). These tests demonstrated that participation in the task and the decisions were no longer significant predictors. All analyses used these transformed variables.

As a precautionary measure, the research team checked if participation in the task or monetary transfer significantly predicted basal physiologic levels as well, perhaps due to some anticipatory effect. Using regression analysis for both participation and the decision that participants made, neither showed any statistically significant effect on any of the five physiologic measures.

Table A1. Measures of the participation in the monetary decision task and the decision itself are unrelated to all physiologic measure for both basal and treatment values.

Hormone	Effect of social task on baseline blood draw (*P* values)	Effect of amount social signal on baseline (*P* values)	Effect of task on second blood-draw levels after removing effects of task (*P* values)	Effect of task on second blood-draw levels after removing effects of social signals (*P* values)
OT	.39	.84	.96	.99
ACTH	.78	.28	.79	.73
NO	.98	.06	.56	.06
BE	.85	.99	.77	.13

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REFERENCES

1. Goodall J. *The Chimpanzees of Gombe: Patterns of Behavior*. Cambridge, MA: The Belknap Press of Harvard University Press; 1986.
2. Goosen C. Social grooming in primates. In: Liss AR, ed. *Comparative Primate Biology. Vol 2, Part B: Behavior, Cognition and Motivation*. New York: Alan R. Liss, Inc; 1986:107–131.
3. Hertenstein MJ, Verkamp JM, Kerestes AM, Holmes RM. The communicative functions of touch in humans, nonhuman primates, and rats: a review and synthesis of empirical research. *Genet Soc Gen Psychol Monog*. 2006;132(1):5-94.
4. Hart S, Field T, Hernandez-Reif M, et al. Anorexia nervosa symptoms are reduced by massage therapy. *Eat Disord. 2001;9(4)*:289-299.
5. Morhenn VB, Park JW, Piper E, Zak PJ. Monetary sacrifice among strangers is mediated by endogenous oxytocin release after physical contact. *Evol Human Behav*. 2008;29:375-383.
6. Berkman LF. The role of social relations in health promotion. *Psychosom Med*. 1995;57(3):245-254.
7. Bosworth HB, Schaie KW. The relationship of social environment, social networks, and health outcomes in the Seattle Longitudinal Study: two analytical approaches. *J Gerontol B Psychol Sci Soc Sci*. 1997;52(5):197-205.
8. Rodríguez-Artalejo F, Guallar-Castillón P, Herrera MC, et al. Social network as a predictor of hospital readmission and mortality among older patients with heart failure. *J Card Fail*. 2006;12(8):621-627.
9. Russell DW, Cutrona CE. Social support, stress, and depressive symptoms among the elderly: test of a process model. *Psychol Aging*. 1991;6(2):190-201.
10. Fratiglioni L, Wang H, Ericsson K, Maytan M, Winblad B. Influence of social network on dementia: a community-based longitudinal study. *Lancet*. 2000;355(9212):1315-1319.
11. Romans SE, Walton VA, Herbison GP, Mullen PE. Social networks and psychiatric morbidity in New Zealand women. *Aust N Z J Psychiatry*. 1992;26(3):485-492.
12. Hanson BS, Isacsson S, Janzon L, Lindell S. Social network and social support influence mortality in elderly men. The prospective population study of "Men born in 1914," Malmö, Sweden. *Amer J Epidemiol*. 1989;130(1):100-111.
13. Obisesan TO, Gillum RF. Cognitive function, social integration and mortality in a U.S. national cohort study of older adults. *BMC Geriatr*. 2009;9:33.
14. Rutledge T, Matthews K, Lui LY, Stone KL, Cauley JA. Social networks and marital status predict mortality in older women: prospective evidence from the study of osteoporotic fractures (SOP). *Psychsom Med*. 2003;65(4):688-694.
15. Kawachi I, Berkman LF. Social ties and mental health. *J Urban Health*. 2001;78(3):458-467.

16. Uchino BN, Cacioppo JT, Kiecolt-Glaser JK. The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms and implications for health. *Psychol Bull.* 1996;119(3):488-531.
17. Hernandez-Reif M, Field T, Krasnegor J, Theakston H. High blood pressure and associated symptoms were reduced by massage therapy. *J Bodywork Mov Ther. 2000;*4:31-38.
18. Olney CM. The effect of therapeutic back massage in hypertensive persons: a preliminary study. *Biol Res Nurs. 2005;7(2):*98-105.
19. Field T, Hernandez-Reif M, Diego M, Schanberg S, Kuhn C. Cortisol decreases and serotonin and dopamine increase following massage therapy. *Int J Neurosci.* 2005;115(10):1397-1413.
20. Field T, Diego M, Hernandez-Reif. Massage therapy research. *Dev Rev.* 2007;27:75-89.
21. Ironson G, Field T, Scafidi F, et al. Massage therapy is associated with enhancement of the immune system's cytotoxic capacity. *Int J Neurosci. 1996;84(1-4):*205-217.
22. Zak PJ. The neurobiology of trust. *Sci Am.* 2008;298(6):88-95.
23. Zak PJ, Kurzban R, Matzner WT. The neurobiology of trust. *Ann N Y Acad Sci.* 2004;1032:224-227.
24. Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol Psychiatry.* 2003;54(12):1389-1398.
25. Zak PJ, Kurzban R, Matzner WT. Oxytocin is associated with human trustworthiness. *Horm Behav.* 2005;48(5):522-227.
26. Barraza JA, Zak PJ. Empathy toward strangers triggers oxytocin release and subsequent generosity. *Ann N Y Acad Sci.* 2009;1167:182-189.
27. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. *Nature.* 2005;435(7042):673-676.
28. Zak PJ, Stanton AA, Ahmadi S. Oxytocin increases generosity in humans. *PLoS One.* 2007;2(11):e1128.
29. Guastella AJ, Mitchell PB, Dadds MR. Oxytocin increases gaze to the eye region of human faces. *Biol Psychiat.* 2008;6(1)3:3-5.
30. Carter CS. Biological perspectives on social attachment and bonding. In: Carter CS, Ahnert L, Grossman KE, Hrdy SB, Lamb ME, Porges SW, Sachser N, eds. *Attachment and Bonding: A New Synthesis.* Cambridge, MA: MIT Press; 2006: 85-100.
31. Odendaal JS, Meintjes RA. Neurophysiological correlates of affiliative behaviour between humans and dogs. *Vet J.* 2003;165(3):296-301.
32. Wikstrom S, Gunnarsson T, Nordin C. Tactile stimulus and neurohormonal response: a pilot study. *Int J Neurosci.* 2003;113(6):787-793.
33. Turner RA, Altemus M, Enos T, Cooper B, McGuiness T. Preliminary research on plasma oxytocin in normal cycling women: investigating emotion and interpersonal distress. *Psychiatry.* 1999;62(2):97-113.
34. Grewen KM, Girdler SS, Amico J, Light KC. Effects of partner support on resting oxytocin, cortisol, norepinephrine, and blood pressure before and after warm partner contact. *Psychosom Med.* 2005;67(4):531-538.
35. Light KC, Grewen KM, Amico JA. More frequent partner hugs and higher oxytocin levels are linked to lower blood pressure and heart rate in premenopausal women. *Biol Psychol.* 2005;69(1):5-21.
36. Ditzen B, Neumann ID, Bodenmann G, et al. Effects of different kinds of couple interaction on cortisol and heart rate responses to stress in women. *Psychoneuroendocrinology.* 2007;32(5):565-574.
37. Holt-Lunstad J, Birmingham WA, Light KC. Influence of a "warm touch" support enhancement intervention among married couples on ambulatory blood pressure, oxytocin, alpha amylase, and cortisol. *Psychosom Med.* 2008;70(9):976-985.
38. Rapaport MH, Schettler P, Bresee C. A preliminary study of the effects of a single session of Swedish massage on hypothalamic-pituitary-adrenal and immune function in normal individuals. *J Altern Complem Med.* 2010;16:1-10.
39. Hanley J, Stirling P, Brown C. Randomised controlled trial of therapeutic massage in the management of stress. *Br J Gen Pract.* 2003;53(486):20-25.
40. Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol.* 2008;51(13):1237-1246.
41. Nielsen NR, Kristensen TS, Schnohr P, Grønbaek M. Perceived stress and cause-specific mortality among men and women: results from a prospective cohort study. *Am J Epidemiol.* 2008;168(5):481-491.
42. Cacioppo JT, Hawkley LC. Social isolation and health, with an emphasis on underlying mechanisms. *Perspect Biol Med.* 2003;46(3 Suppl):S39-52.
43. Seeman TE. Health promoting effects of friends and family on health outcomes in older adults. *Am J Health Promot.* 2000;14(6):362-370.
44. Gallagher TF, Yoshida K, Roffwarg HD, Fukushima DK, Weitzman ED, Hellman L. ACTH and cortisol secretory patterns in man. *J Clin Encdocr Metab.* 1973;36(6):1058-1068.
45. Follenius M, Simon C, Brandenberger G, Lenzi P. Ultraradian plasma corticotrophin and cortisol rhythms: time-series analyses. *J Endocrinol Invest.* 1987;10(3):261-266.
46. Day JA, Mason RR, Chesrown SE. Effect of massage on serum level of β-endorphin and β-lipotropin in healthy adults. *Phys Ther.* 1987;67(6):926-930.
47. Foley KM, Kourides IA, Inturrisi CE, et al. β-endorphin: analgesic and hormonal effects in humans. *Proc Natl Acad Sci U S A.* 1979;76(10):5377-5381.
48. Mooncey S, Giannakoulopoulos X, Glover V, Acolet D, Modi N. The effect of mother-infant skin-to-skin contact on plasma cortisol and β-endorphin concentrations in preterm newborns. *Infant Behav Dev.* 1997;20:553-557. [cannot find source, author to provide copy of article].
49. Kaada B, Torsteinbø O. Increase of plasma β-endorphins in connective tissue massage. *Gen Pharmacol.* 1989;20(4):487-489.
50. Keverne EB, Martensz ND, Tuite B. Beta-endorphin concentrations in cerebrospinal fluid of monkeys are influenced by grooming relationships. *Psychoneuroendocrinology.* 1989;14(1-2):155-161.
51. Van Ree JM, Niesink JM. Low doses of β-endorphin increase social contacts of rats tested in dyadic encounters. *Life Sci.* 1983;33:611-614.
52. Buga GM, Gold ME, Wood KS, Chaudhuri G, Ignarro LJ. Endothelium-derived nitric oxide relaxes nonvascular smooth muscle. *Eur J Pharmacol.* 1989;161(1):61-72.
53. Lowenstein CJ, Dinerman JL, Snyder SH. Nitric oxide: a physiologic messenger. *Ann Intern Med.* 1994;120(3):227-237.
54. Murray PR, Rosenthal KS, Pfaller MA. *Medical Microbiology.* 6th ed. Philadelphia, PA: Mosby; 2009.
55. Morhenn VB. Firm stroking of human skin leads to vasodilation possibly due to the release of substance P. *J Dermatol Sci.* 2000;22(2):138-144.
56. Taylor SE, Saphire-Bernstein S, Seeman TE. Are plasma oxytocin in women and plasma vasopressin in men biomarkers of distressed pair-bond relationships? *Psychol Sci.* 2010;21(1):3-7.
57. Mendez A. Assay procedures. Presented at: Pittsburgh Mind-Body Center Workshop on Oxytocin; April 27, 2010; Pittsburgh, PA.
58. Larson RJ, Diener E. Affect intensity as an individual difference characteristic: a review. *J Res Personality.* 1987;21:1-39.
59. Snyder M. *Public Appearances/Private Realities: The Psychology of Self-monitoring.* New York, NY: W. H. Freeman and Company; 1987.
60. Fraley RC, Waller NG, Brennan KA. An item-response theory analysis of self-report measures of adult attachment. *J Pers Soc Psych.* 2000;78(2):350-365.
61. Zak PJ, Borja K, Matzner W, Kurzban R. The neuroeconomics of distrust: sex differences in behavior and physiology. *Am Econ Review.* 2005;95:360-364.
62. Challinor SM, Winters SJ, Amico JA. Pattern of oxytocin concentrations in the peripheral blood of healthy women and men: effect of the menstrual cycle and short-term fasting. *Endocr Res.* 1994;20(2):117-125.
63. Zak PJ. The physiology of moral sentiments. *J Econ Behav Org.* 2011;77:53-65.
64. Suh BY, Liu JH, Rasmussen DD, Gibbs DM, Steinberg J, Yen SS. Role of oxytocin in the modulation of ACTH in women. *Neuroendocrinology.* 1986;44(3):309-313.
65. Chiodera P, Salvarani C, Bacchi-Modena A, et al. Relationship between plasma profiles of oxytocin and adrenocorticotropic hormone during suckling or breast stimulation in women. *Horm Res.* 1991;35(3-4):119-123.
66. Parker KJ, Buckmaster CL, Schatzberg AF, Lyons DM. Intranasal oxytocin administration attenuates the ACTH stress response in monkeys. *Psychoneuroendocrinology.* 2005;30(9):924-929.
67. Page SR, Ang VT, Jackson R, White A, Nussey SS, Jenkins JS. The effect of oxytocin infusion on adenophypophyseal function in man. *Clin Endocrinol* (Oxf).1990;32(3):301-313.
68. Robinson AG, Verbalis JG. Posterior pituitary gland. In: Larson PR, Kronenberg HM, Melmed S, Polonsky KS. *Williams Textbook of Endocrinology.* Philadelphia, PA: Saunders; 2003: 281-89.
69. Vankrieken L, Godart A, Thomas K. Oxytocin determination by radioimmunoassay. *Gynecol Obstet Invest.* 1983;16(3):180-185.
70. Blatter LA, Taha Z, Mesaros S, Shacklock PS, Wier WG, Malinski T. Simultaneous measurements of Ca2+ and nitric oxide in bradykinin-stimulated vascular endothelial cells. *Circ Res.* 1995;76(5):922-924.
71. Kanai AJ, Strauss HC, Truskey GA, Crews AL, Grunfeld S, Malinski T. Shear stress induces ATP-independent transient nitric oxide release from vascular endothelial cells, measured directly with a porphyrinic microsensor. *Circ Res.* 1995;77(2):284-293.
72. Becker JB, Breedlove MS, Crews D, McCarthy MM, eds. *Behavioral Endocrinology.* Cambridge, MA: The MIT Press; 2002.
73. Rasmussen NA, Farr LA. Beta-endorphin response to an acute pain stimulus. *J Neurosci Methods.* 2009;177(2):285-288.
74. Reis WL, Giusti-Paiva A, Ventura RR, et al. Central nitric oxide blocks vasopressin, oxytocin and atrial natriuretic peptide release and antidiuretic and natriuretic responses induced by central angiotensin II in conscious rats. *Exp Physiol.* 2007;92(5):903-911.
75. Cacioppo JT, Patrick W. *Loneliness: Human Nature and the Need for Social Connection.* New York: WW Norton & Company, Inc; 2008.
76. Szeto A, Nation DA, Mendez AJ, et al. Oxytocin attenuates NADPH-dependent superoxide activity and IL-6 secretion in macrophages and vascular cells. *Am J Physiol Endocrinol Metab.* 2008;295(6)5:E1495-1501.
77. Yoshida M, Takayanagi Y, Inoue K, et al. Evidence that *oxytocin* exerts anxiolytic effects via *oxytocin* receptor expressed in serotonergic neurons in mice. *J Neurosci.* 2009;29(7):2259-2271.
78. Scantamburio G, Hansenne M, Fuchs S, et al. Plasma oxytocin levels and anxiety in patients with major depression. *Psychoneuroendocrinology.* 2007;32(4):407-410.
79. Uvnäs-Moberg K, Björkstrand E, Hillegaart V, Ahlenius S. Oxytocin as a possible mediator of SSRI-induced antidepressant effects. *Psychopharmacology* (Berl).1999;142(1):95-101.