Influence of a "Warm Touch" Support Enhancement Intervention Among Married Couples on Ambulatory Blood Pressure, Oxytocin, Alpha Amylase, and Cortisol

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Objective: To investigate whether a support intervention (warm touch enhancement) influences physiological stress systems that are linked to important health outcomes. Growing evidence points to a protective effect of social and emotional support on both morbidity and mortality. **Methods:** In this study, 34 healthy married couples ($n = 68$), aged 20 to 39 years (mean = 25.2 years), were randomly assigned to a "behavior monitoring" control group or participated in a 4-week intervention study in which clinic levels of plasma oxytocin, 24-hour ambulatory blood pressure, and salivary cortisol and alpha amylase were obtained pre and post intervention, at the same time salivary oxytocin was taken at home during weeks 1 and 4. **Results:** Salivary oxytocin was enhanced both early and late in the intervention group and alpha amylase was reduced at post treatment in intervention group husbands and wives relative to controls. Husbands in the intervention group had significantly lower post treatment 24-hour systolic blood pressure than the control group. **Conclusion:** Increasing warm touch among couples has a beneficial influence on multiple stress-sensitive systems. **Key words:** ambulatory blood pressure, oxytocin, alpha amylase, cortisol, social support, cardiovascular functioning, health.

BP = blood pressure; **ABP** = ambulatory blood pressure; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **OT** = oxytocin; **HPA** = hypothalamic-pituitary adrenocortical; **SNS** = sympathetic nervous system; **AUC** = area under the curve.

INTRODUCTION

Epidemiological research indicates that both the quality and quantity of social relationships may significantly protect individuals from various causes of morbidity and mortality. For most adults, marriage plays a central role in their lives even as compared with other social relationships. For example, emotional support from a spouse is related to lower risk of cardiovascular and all-cause mortality (1–4). Because increasing emotional support among couples may be beneficial both physically and psychologically, studies testing simple, low cost, couple-based intervention methods designed to enhance emotional support and examining whether such interventions have physical and psychological benefits are thus important to do.

Although there are many ways in which emotional support may be conveyed, a relatively less studied means of expressing emotional support and affection important for couples is through nonsexual, caring physical touch, such as hand-holding, hugs, and sitting or lying "cuddled up" (5–7). A number of experts (3,8–12) have hypothesized that enhanced oxytocin (OT) activity is a logical candidate to be one of the primary physiological mediators of the health benefits of emotional support, particularly those linked to the types of warm touch mentioned above. Studies in animals confirm that OT administration or enhancing natural OT activity through repeated daily massage-like stroking leads to prolonged decreases in blood pressure (BP) and stress hormone levels (13–20). In humans, however, a single bout of massage performed by a massage therapist has not consistently elicited increases in measures of OT (21,22). Recently, Ditzen et al. (23) found that a single 10-minute bout of shoulder and neck massage performed by husbands did not increase their wives' plasma OT responses to a subsequent social stressor, although this touch-based support (but not verbal support) by the men did reduce the women's stress-related cortisol and heart rate (HR) increases. Likewise, augmenting OT through exogenous administration has been found to enhance the stress buffering effect of social support (24). In that study, the combination of support from a friend plus intranasal OT led to greater calmness and lower cortisol response to social stress than either intervention alone.

We believe greater OT is linked to lower stress hormone levels and lower BP, and that endogenous OT activity is more powerfully enhanced by the cumulative effect of regular and repeated warm touch rather than a single exposure. This interpretation is consistent with prior findings by Light and colleagues (25), indicating that among 59 premenopausal women, those who reported receiving more frequent hugs from their spouses at home had higher plasma OT levels obtained just before they spent 10 minutes cuddling with their husbands in the laboratory. In these 59 women, higher OT was also linked to lower systolic blood pressure (SBP) levels, but not to reduced BP reactivity to stress. In a second study where no stressors occurred (26), higher OT levels before and after 10 minutes of warm cuddling time with their partners were shown by both men and women who reported having more supportive partners. In the women, this higher OT was also associated with lower sympathetic activity as indexed by plasma norepinephrine levels.

Thus, we hypothesized that couple-based emotional support training that enhanced warm physical contact between marital partners and emphasized warm touch as a way of communicating affection and support may induce increases in OT activity and decreases in BP and stress hormones when the warm touch techniques are practiced on a regular basis in the context of communicating affection and caring support. Spe-

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cifically, in the present study, we compared pretreatment versus posttreatment measures of sympathetic activity as indexed by salivary alpha amylase, of hypothalamic-pituitary adrenocortical (HPA) activity as indexed by salivary cortisol, of 24-hour ambulatory blood pressure (ABP), and OT measures taken during the first and last week of treatment in couples who did versus those who did not undergo one session of training in listening touch based on the types of touch used in Rosen Method Bodywork (27,28) and one training session in head, neck, and shoulder massage. The intervention couples then practiced these warm touch techniques for 30 minutes ≥3 times per week for 4 weeks whereas the control group couples simply monitored their own touch behaviors by keeping a diary record and reporting it online each week for the same 4 weeks. Cortisol is a well-established indicator of HPA-axis activity, and alpha amylase has been touted as a useful saliva-based marker of sympathetic adrenal medullary activity, sensitive to increasing and decreasing stress, and correlated with plasma norepinephrine levels but able to be obtained noninvasively in the home environment (29,30). Prior studies of the beneficial physiological effects of massage have indicated that BP levels are decreased for a few minutes (31), but no prior study to our knowledge has employed 24-hour ABP monitoring. Although a transitory decrease in BP immediately after massage is interesting, it is less meaningful to long-term cardiovascular outcomes than a reduction in 24-hour BP levels, which have been shown to be a strong predictor of morbidity and mortality (32–34). We hypothesized that couples who participated in the support (couple contact enhancement) intervention would show increases in OT and decreases in ABP, cortisol, and alpha amylase over the 4-week period as compared with those in the nonintervention "monitoring only" comparison group.

METHODS

Participants

To test this, 36 healthy married couples (n = 72) were recruited from the community (age = 25.2 ± 3.8 years (mean ± standard deviation (SD)); range = 20–39 years; body mass index (BMI) = 24.07 ± 4.33, range 16.5–37.3). To qualify, couples were married at least 6 months. Participants were paid $160 each as compensation. Consistent with prior research (33), the following self-reported inclusion criteria were used to select healthy participants: no existing hypertension, no prescription medication use except contraceptives, no past history of chronic disease with a cardiovascular (e.g., diabetes) or immune (e.g., cancer) component, and no recent history of psychological disorder (e.g., major depressive disorder). Volunteers were also excluded if pregnant, nursing, within 6 months postpartum, or planning to become pregnant within the time frame of the study. Of the initial qualifying couples, two couples' data were dropped, one due to a death in the family and the other because the wife became pregnant. Thus, our final sample consisted of 34 couples (n = 68). Couples were randomized into two groups via a random numbers table, with 20 couples in the intervention group and 14 couples in the "monitoring only" control group. Recruitment of subjects and study protocol were approved by the university Institutional Review Board committee.

Procedures

After randomization, couples in both groups underwent similar physiological assessment procedures before and after the 4-week intervention/behavioral monitoring period. Both pre and post intervention, ABP was monitored for 24 hours, and at specific time points spaced throughout those same 24-hour periods, five saliva samples for cortisol and alpha amylase were obtained. Plasma OT was obtained once pre and post intervention. The effects of the intervention on OT activity were also assessed by comparing salivary OT obtained at home once during week 1 and twice during week 4 of the intervention/monitoring period. Data collection occurred within participation cohorts (consisting of approximately eight couples per cohort) between fall 2005 and summer 2007. Interested participants were first screened over the phone to determine if they met the inclusion criteria. Qualified participants were scheduled to come into the laboratory in the morning. On arrival in the laboratory (after consent was obtained), participants completed a packet of questionnaires that assessed standard variables that may influence health (e.g., demographics, health history). Height and weight were obtained on a standard medical scale (e.g., Health-O-Meter) to ensure accurate measures of BMI. Participants then received verbal and written instructions on saliva collection, and a saliva sample was taken to ensure they knew how to properly collect the saliva and obtain a morning sample. Each participant was asked to collect saliva four additional times during the next 24 hours. Thus, there were a total of five salivary samples obtained throughout the 24-hour period. These five samples were used for assay of both cortisol and alpha amylase. Researchers then took three BP measurements, each 1 minute apart as a baseline reading. Participants were then given instructions for ambulatory monitoring and had the monitor placed on them by a trained research assistant. For validation purposes, a minimum of three readings from the ambulatory monitor were compared against a sphygmomanometer, using a T-tube adapter. Readings were considered valid if three consecutive readings matched up (±5 mm Hg). After the participants left the laboratory, they continued to wear the ABP monitor throughout the day and night as they were going about their normal activities. They returned to the laboratory 24 hours later. The identical ABP and saliva sampling procedure was repeated approximately 4 weeks later post intervention.

To ensure that the control and intervention groups did not differ in OT levels before the study, a single-stick pretreatment blood draw for plasma OT obtained via venipuncture was made after each couple sat close together for 5 minutes holding hands. Additional saliva samples were obtained at home on three occasions for the purposes of obtaining salivary OT. The first OT saliva sample was taken during the first week of the intervention/monitoring period. The second and third samples were both taken during the fourth week of the intervention/monitoring period, on different days. The intervention couples were instructed to obtain all three saliva samples at home on evenings when they practiced the warm touch techniques, whereas the controls were simply told to collect their samples during evenings spent at home. All couples were called by a research assistant during this time and reminded to do this. Participants were instructed on how to keep the samples in a frozen state and then all three samples were returned to the laboratory at the time of the postintervention procedure.

Outline of Intervention, Home Practice, and Postintervention Testing Protocol

Intervention

After the 24-hour ABP procedure, couples randomized to the intervention group were asked to come into the laboratory in groups of three to five couples, for a 1-hour session to describe and allow hands on practice of Couple Contact Enhancement techniques. In Couple Contact Enhancement, subjects came in twice for training. During the first session (week 1 of the intervention), couples were trained in Rosen Method Listening Touch. A male and female staff member led couples through examples of "listening touch" skills where one increases awareness of the partner's mood and body state through touching their partner's neck, shoulders, and hands, first while the partner was seated in front of them and then while both partners stood together back to back, gradually initiating a slow rocking motion. Couples were then asked to "role play" these skills, with partners alternating in the roles of warm touch giver and touch recipient. Then, they were given an audio recording to guide them in practicing these techniques at home, and were instructed to practice for 30 minutes three times/week for 4 weeks, and to keep records of when they practiced and their mood state before and after practice. During the second session (week 2 of the intervention), couples watched a short video of

actors showing examples of sensitive and insensitive touch, followed by a second video demonstrating neck, forehead, and shoulder massages. Couples were then asked to follow along with the massage video, practicing with their spouse under supervision of a trained staff member. Couples were given the option either to add massage to their practice or to replace the listening touch practice with massage during weeks 2 to 4. In the control group, subjects were told not to change anything about their normal behavior with their spouse and to simply keep a diary of their physical affection and mood. They were asked to report this once a week for 4 weeks. For both the intervention and control groups, monitoring of warm touch had to be recorded online on a fixed schedule to prevent confabulation errors associated with retrospective recall. The control couples were informed of the purpose of the study and that they were in the control group to alleviate any pressure to increase physical touch within the relationship. To discourage dropping out of the control group, these couples were given the opportunity to receive the couple-contact enhancement intervention at the completion of the study. Postintervention Testing was the same as time 1 procedures for ABP and saliva sampling.

Measures

Medical and Demographic Information (Volunteer Health Questionnaire)

Subjects completed an in-house form assessing all relevant health variables, plus occupation, education, and total family income.

Cardiovascular

Cardiovascular functioning was measured using ambulatory (portable) BP techniques. The Accutracker II (Suntech Medical Instruments, Raleigh, North Carolina) was used to estimate ambulatory readings of SBP, diastolic blood pressure (DBP), and HR. The Accutracker II was designed specifically for ambulatory assessments and is well validated as readings correspond with intra-arterial BP assessments during rest, isometric exercise, and bicycle exercise (35,36). The monitor was set to randomly take three readings per hour during the day or waking hours (6 AM–10:59 PM) and two readings per hour during the night (11 PM–6 AM).

The Accutracker II utilizes a number of codes that may signify problems with the estimation of the ambulatory cardiovascular assessment. Based on prior research (37), we deleted readings associated with test codes 2 (weak Korotkoff sounds), 3 (microphone difficulties), and 7 (airleaks). Outliers associated with artifactual readings were also identified using the criteria by Marler and colleagues (38). These variables included: a) SBP $<$70 mm Hg or $>$250 mm Hg; b) DBP $<$45 mm Hg or $>$150 mm Hg; c) HR $<$40 beats/minute or $>$200 beats/minute; and d) SBP/DBP $<$[1.065 + (0.00125 $\times$ DBP)] or $>$3.0.

OT Sampling and Bioassay Procedures

A pre- and posttreatment plasma sample for OT was obtained directly from a single-stick venipuncture after 5 minutes of close warm couple contact, and the three home saliva samples for OT were obtained by using unstimulated passive drool collected into 4-ml plastic tubes. Participants were asked to spit into the tube until full. Samples were immediately frozen at the subjects' homes, transported still frozen to the laboratory, and then shipped to the University of North Carolina for assay using enzyme immunoassay (EIA) methods (OT EIA kit, Assay Designs, Ann Arbor, Michigan). For salivary OT, the methods used were similar to those developed for salivary OT and validated by Carter et al. (39), with the addition of an extraction step that was required because Assay Designs is now using a new and different OT antibody from the one they used. This new OT antibody now requires an extracted sample because, as stated in the new kit instructions, this new antibody gives much lower precision without an extracted sample. The extraction reduces matrix interference and, through evaporation, concentrates the sample 3.2 times, which is very similar to the 4.0 times concentration produced by the full dry-down procedure by Carter and colleagues (39). There are differences in absolute OT levels obtained with this antibody, reagents and extraction step from levels reported in previous studies, even those that used the older Assay Designs kits, because the absolute values are dependent on the antibody and whether an extraction and/or dry-down procedure was done, and the type of this procedure. Values with the old Assay Designs antibody without extraction tended to be much higher, i.e., $>$15 to 300 pg/ml. These values from the old antibody compare with values of 2 to 40pg/ml with extracted samples and the new antibody. Our UNC Assay Laboratory has used this same new OT antibody to perform assays from plasma samples drawn from women in labor with the current reagents and extraction where the levels obtained were in the range of 30 to 189 pg/ml, which may provide a perspective on the higher values of the normal range with this current method. Details on the OT extraction and assay methods, which were the same for both saliva and plasma samples, are given in Appendix A. In this study, the extraction efficiency was 101.6% and intra assay variability was 4.8% obtained from both saliva and plasma samples because all of these samples were extracted and assayed in the same batch at the same time.

Limited evidence has been obtained by our co-author (K.C.L.) supporting the position that salivary OT measures determined by this modified assay method can provide accurate results. Using 28 plasma and 28 saliva samples obtained within 2 to 3 minutes of each other from women at rest, with all samples extracted and assayed in one batch using the same methods described above, Grewen and Light (personal communication, 2008) found that concurrent plasma and saliva OT levels were significantly correlated with a moderately good degree of association ($r = .52$, $p < .0049$).

Salivary Cortisol and Alpha Amylase

Consistent with standard salivary sampling procedures, we sampled at standardized times to account for diurnal effects. Samples were obtained at 7 AM, 12 PM, 5 PM, 10 PM, and on wakening, before they got out of bed. Samples were obtained by using a Salivette, a standard sampling product (Sarstedt, Inc., Newton, North Carolina). Participants were instructed to suck or chew on a cotton roll until it was saturated (very soggy—usually about 2–3 minutes, 1 minute minimum). The cotton roll was then placed inside a retainer and then in the centrifuge tube. To minimize potential contamination, participants were told not to eat a major meal within 60 minutes before sample collection, to avoid alcohol for 24 hours before sample collection, and to avoid dairy products during the 30 minutes before sample collection. We also informed them to be careful about acidic or high sugar foods and that ideally they should rinse their mouth thoroughly with water 10 minutes before giving a sample to minimize the potential for saliva contamination. Because of potential blood contamination, we also recommended that they not brush their teeth within 3 hours before sample collection.

Saliva samples were stored in a freezer (-20°C) until shipped on dry ice for assay. After thawing, salivettes were centrifuged at 3000 rpm for 5 minutes, which resulted in a clear supernatant of low viscosity. Salivary cortisol was measured with a commercial immunoassay with chemiluminescence detection (CLIA, IBL-Hamburg, Germany). The assay has a lower detection limit of 0.1 nmol/l with intra- and interassay coefficients of variations $<$8%. Details on the alpha amylase assay methods, which are less well known, are given in Appendix B.

Primary Analyses

We used Proc Mixed (SAS Institute, Cary, North Carolina) (40) to estimate random intercept models with random effects for couples. Kenny and colleagues (41) proposed a model of dyadic data analysis that uses the dyad as the unit of analysis. This model suggests that a person's independent variable score affects both one's own dependent variable score (i.e., actor effect) and the partners' dependent variable score (partner effect). As such, analyses directly model the interdependence of husbands' and wives' data. In our analyses, gender and intervention condition were first centered at their grand mean before inclusion into the model (42). Separate analyses were performed examining the impact of the intervention and its statistical interaction with gender on post intervention, salivary alpha amylase, salivary cortisol, and ABP levels controlling for relevant preintervention assessments. For the five preintervention and five postintervention samples of alpha amylase and cortisol, area under the total response curve with respect to the ground (AUC_G) was calculated using the trapezoid formula following Pruessner and colleagues (43). Due to nonnormal (skewed) distribution of the alpha amylase data, this measure was log transformed before final data analysis. For salivary OT, all samples were obtained at home after the interven-

TABLE 1. Sample Characteristics Preintervention by Group Assignment

	Intervention (n = 40)		Control (n = 28)		
	Mean	SEM	Mean	SEM	p
Age (years)	26.18	0.80	23.79	0.94	.06
BMI	24.32	0.79	23.74	0.91	.63
24-hr SBP, mm Hg	112.10	1.20	111.93	1.43	.93
24-hr DBP, mm Hg	67.90	0.75	66.75	0.89	.33
Log AUC alpha amylase, U/ml	6.58	0.14	6.73	0.18	.52
AUC salivary cortisol, nmol/l	147.40	9.84	155.71	11.88	.59
Plasma oxytocin, pg/ml	9.94	1.20	7.53	1.43	.21

SEM = standard error of the mean; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; AUC = area under the curve.
The p values are based on two-tailed tests.

TABLE 2. Raw (Unadjusted) Salivary OT Levels by Group Assignment

	Intervention (n = 40)		Control (n = 28)		
	Mean	SEM	Mean	SEM	p
Salivary OT pg/ml: week 1	14.73	1.41	6.52	1.80	<.0001
Salivary OT pg/ml: week 4	16.22	1.21	6.92	1.41	<.0001

SEM = standard error of the mean; OT = oxytocin.
The p values are based on two-tailed tests.

tion or monitoring period had begun. Because we wanted to examine whether a single week of enhanced warm contact was sufficient to increase OT activity, we first compared week 1 salivary OT levels between the intervention and control groups. Then, to examine whether additional warm contact can sustain or even lead to greater increases in OT activity, group differences in the mean of samples 2 and 3 obtained during the final week of the intervention or monitoring period were examined before and after controlling for week 1 OT levels. Correlations between physiological measures were computed as Pearson product-moment correlations. Data are reported in unstandardized regression coefficients.

RESULTS

Preintervention Comparisons Between Groups

Table 1 represents the baseline characteristics of our groups. The randomized groups did not differ with respect to mean BMI; however, there was a trend toward group differences on age (p = .06).[1] The randomized groups also did not differ with respect to preintervention 24-hour SBP, DBP, plasma OT,[2] salivary alpha amylase, or cortisol. We did find a gender effect for pretreatment 24-hour SBP, such that husbands in both groups did have significantly higher pretreatment 24-hour SBP levels than their wives (118.9 versus 104.9 and 117.2 versus 107.0 for control and intervention groups, respectively; $p < .01$).

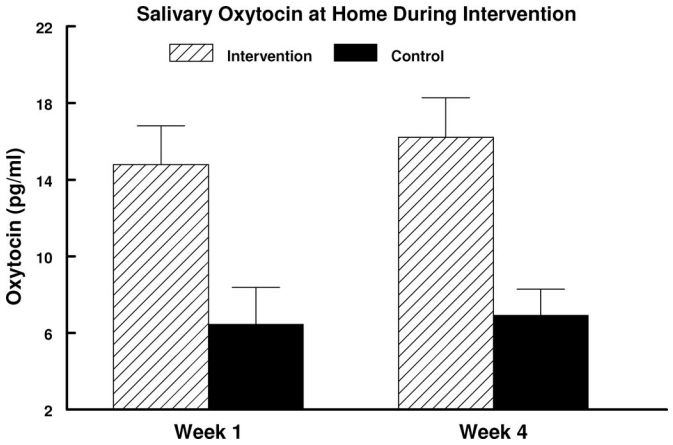

Figure 1. Salivary oxytocin obtained at home during week 1 and week 4 of the study in the intervention versus the control groups, collapsed across both genders. Intervention couples had higher home oxytocin levels than control couples at both week 1 and week 4 ($p < .001$).

Impact of Couples Support Intervention on Physiology

We found no main effect of the intervention on ambulatory SBP or DBP, salivary cortisol, or plasma OT. In contrast to plasma OT values obtained after needle stick in the clinic which did not differ from pre- to posttreatment (mean values = 9.94 versus 9.07 in the intervention group and 7.53 versus 7.10 in the control group; p = .26), we did find a significant effect of the intervention for salivary OT obtained at home during the month of treatment/monitoring that was independent of gender (b = 2.57; $p < .01$). Even as early as intervention week 1, salivary OT levels were significantly higher in the intervention group versus the control group (b = 4.14; p = .001) (Table 2). Both men and women in the intervention condition continued to have higher OT levels than those in the monitoring control condition during the final week as well (Figures 1 and 2). This effect remained significant after adjusting for pretreatment plasma OT (b = 4.57; $p > .0001$) and even after adjusting for their higher week 1 OT levels ($p < .01$), indicating that further significant albeit modest increases in OT activity occurred with greater exposure to the warm touch intervention.[3]

We next examined the influence of the intervention on alpha amylase. Results revealed a significant effect of the

[1]All primary analyses were repeated including age as a covariate. None of the findings changed significance.

[2]Importantly, pretreatment plasma OT is significantly correlated with salivary OT taken the first week of treatment (r = .32; $p < .01$). Upon further inspection of normal plots, we identified that plasma OT was skewed with a few high outliers. When we log-transformed the plasma OT data, the association between pretreatment plasma OT and week 1 saliva OT was strengthened (r = .38; p = .002).

[3]Similarly, analyses using a change score (change from week 1 to week 4 salivary OT) were significantly higher among the intervention group than the control group when controlling for week 1 salivary OT ($F(1,31) = 9.88$; $p < .005$) and preintervention levels of plasma OT ($F(1,31) = 4.80$; $p < .05$).

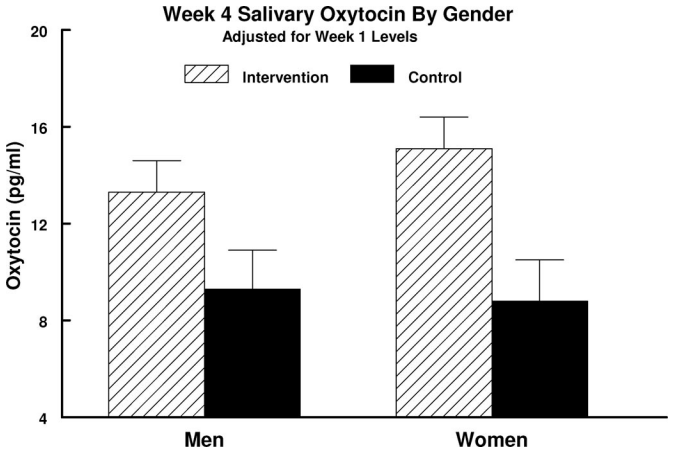

Figure 2. Salivary oxytocin levels of husbands and wives depicted separately in week 4 adjusted for levels at week 1, with the group differences reflecting the added effect of additional intervening practice of warm touch techniques. No gender differences were observed, but the intervention group had significantly greater enhancement of oxytocin responses at the end of training versus the control group ($p < .01$).

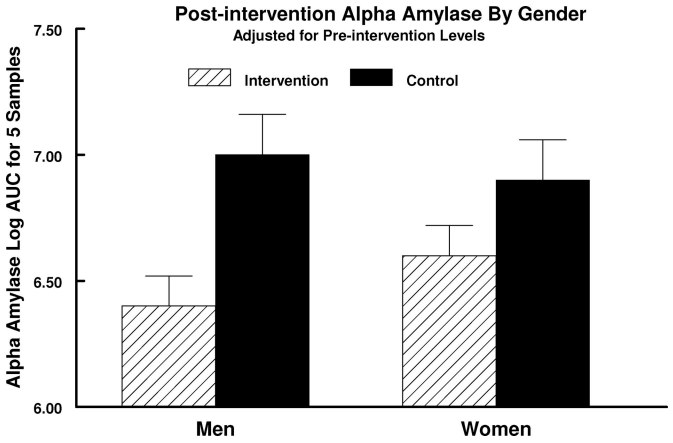

Figure 3. Posttreatment log-scaled salivary alpha amylase levels based on area under the curve (AUC) of five samples obtained throughout a single day of home monitoring, and adjusted for pretreatment levels. No gender differences were observed, but the intervention group had significantly decreased posttreatment levels versus the control group ($p < .01$).

log-transformed alpha amylase data ($b = -0.20$; $p = .01$). Thus, after controlling for pretreatment levels, posttreatment alpha amylase was significantly lower among husbands and wives in the intervention group than those in the control group (Figure 3). Note that these intervention-related differences are in log units, and thus, numerically small differences actually reflect a relatively large magnitude effect if expressed in raw values (908 versus 1216 or a 34% difference, collapsing across gender groups).

Does the Effect of the Intervention Differ for Husbands and Wives?

To answer this question, we examined the statistical interaction between gender and intervention/control condition for each of our physiological dependent measures taken post intervention after controlling for the subject's levels of that

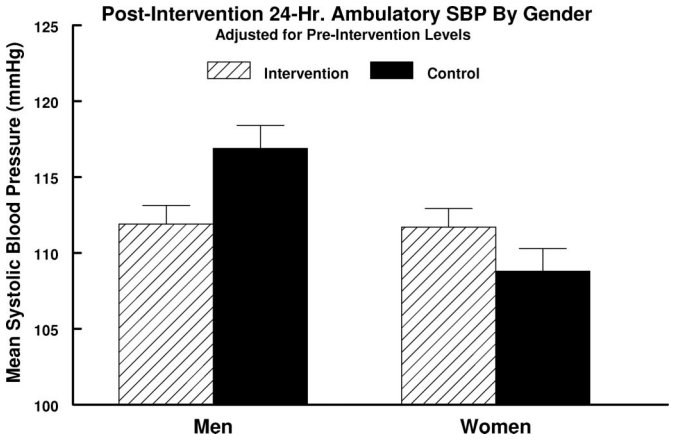

Figure 4. Posttreatment 24-hour ambulatory systolic blood pressure (SBP) levels adjusted for pretreatment levels. A significant interaction with gender was observed ($p < .003$). After treatment, SBP levels in the intervention group husband decreased to levels that did not differ reliably from the wives in either treatment group but were significantly lower ($p < .01$) than control group husbands, who maintained posttreatment SBP levels than the wives ($p < .0005$).

same measure obtained pre intervention. For OT, this was accomplished examining week 4 salivary OT controlling for week 1 salivary OT. We found no significant interaction effect for OT, cortisol or alpha amylase; however, there was a significant gender × condition interaction for 24-hour ambulatory SBP ($b = -1.99$; $p = .003$). Contrasts revealed that there was no significant difference for wives between the two treatment conditions. For husbands, however, the effect of conditions did significantly influence ambulatory SBP ($b = -2.49$; $p = .006$). Husbands in the control group had higher postintervention SBP than husbands in the intervention condition, after controlling for preintervention SBP ($p < .01$). Also, husbands in the control condition had higher SBP than the wives in either condition ($p < .01$), whereas husbands in the intervention condition did not differ from the wives in their postintervention SBP (Figure 4). The statistical interaction between intervention group and gender did not reach significance for 24-hour DBP ($b = -0.67$; $p = .11$).

Is Increased OT Linked to Decreased Sympathetic Activity as Indexed by Alpha Amylase?

We first examined the Pearson correlation coefficients and found that postintervention alpha amylase and week 4 OT were significantly and inversely correlated ($r = -27$; $p = .03$). We next performed similar Proc Mixed analyses to examine any potential relationship between these measures at the same time controlling for gender, preintervention alpha amylase, and week 1 OT. We found no independent effect of preintervention alpha amylase on OT; however, there was a marginally significant relationship between postintervention alpha amylase and week 4 OT ($b = -2.77$; $p = .07$). Thus, after the intervention, subjects with higher OT levels tended to have lower alpha amylase levels. However,

when we add intervention group as a covariate, the effect is eliminated ($p = .25$).

Is Postintervention SBP Linked to Decreased Alpha Amylase or to Increased OT?

To examine whether posttreatment alpha amylase and week 1 or week 4 OT were related to posttreatment changes in ambulatory SBP, we used Proc Mixed and adjusted for preintervention SBP and gender. For alpha amylase, we obtained a marginal effect when both husbands and wives were included ($b = 2.27$; $p = .07$). When we examined this association only among husbands (where we found the greatest effect of the intervention on SBP), we found a significant relationship between time 2 alpha amylase and time 2 ambulatory SBP ($b = 2.88$; $p = .03$). Thus, lower posttreatment alpha amylase in husbands was associated with greater decreases in SBP. In contrast, we failed to find a significant effect of either OT measure on postintervention ambulatory SBP.

DISCUSSION

The primary aim of this study was to determine whether increasing supportive interactions in married couples via a simple training intervention and home practice could have a direct influence on identified physiological pathways that inform health. More specifically, we compared pretreatment versus posttreatment measures of sympathetic activity as indexed by salivary alpha amylase, HPA activity as indexed by salivary cortisol, plasma OT, and 24-hour ABP in couples who were randomized to training in warm listening touch and massage versus to a "monitoring only" control condition. We also compared OT responsivity as indexed by salivary OT obtained at home in the evening during the first week and fourth week of home practice/monitoring in these two groups. The results of this study indicate that both husbands and wives who participated in the intervention had greater decreases in alpha amylase at the posttreatment follow-up (adjusting for pretreatment levels) compared with couples in the control group. Because the saliva samples were obtained at intervals throughout a normal day, this observation is consistent with the interpretation that both husbands and wives in the intervention group experienced beneficial reductions in sympathetic activation as they dealt with their usual life demands. For ABP, the positive effect of the intervention seemed to be more salient among husbands than among wives. Although at pre treatment, husbands in the intervention group had mean ambulatory SBP levels similar to husbands in the control group, with both groups of men having higher levels than the wives; at post treatment, husbands in the intervention group had significantly lower 24-hour ambulatory SBP and no longer differed from the women. We hypothesize that our failure to see a similar effect of the intervention on ambulatory SBP in the women was due to a floor effect; their preintervention BP levels were quite low, as is typical of women at this young age. In regard to OT, we found that both men and women in the intervention group had higher levels at home during both the first and last weeks of the home practice/monitoring period, and the effect of continued home practice was to further enhance OT response over the weeks of practice. It is noteworthy that the salivary OT samples were specifically obtained on days when the couples practiced their warm touch techniques, which may account for the large group differences obtained even in the initial week.

Although postintervention SBP and salivary OT were not significantly related to each other (even in men), both were related to decreased sympathetic activity as indexed by salivary alpha amylase. Thus, our findings do not provide support for the interpretation that greater OT activity induced by our intervention directly mediates the lower SBP observed in the husbands after the intervention, although they are in part consistent with the possibility that lower sympathetic activity associated with higher OT activity may mediate the reduced SBP in men. However, we acknowledge that, because our saliva samples for OT were obtained only once per day in the evening and the alpha amylase samples were obtained throughout the day, as was the ambulatory SBP, our methods may have made it more likely to observe associations between the latter two measures.

We found no effect of the intervention on cortisol, or any reliable association between cortisol and OT. This is inconsistent with our hypotheses and with a large animal literature and a modest human literature relating OT to lower HPA axis activity (24,44,45). Whereas cortisol has been widely used as an index of HPA activity, perhaps other measures may have been a better test. It is also possible that we did not have enough power to detect such effects due to our modest sample size.

We also found no effect of the intervention on plasma OT. Although it is unclear why the intervention would result in null findings for plasma OT but was significantly associated with salivary OT, it is possible that the stress induced by the venipuncture immediately before taking the plasma sample caused an increase in OT in some participants, thereby obscuring the effect of treatment group differences. However, another factor to consider is that saliva samples were taken closer in time to the intervention practice sessions and so they were more sensitive to its influence. Thus, a potential alternative explanation for these differing OT findings (saliva versus plasma) is that there might not be a chronic change in OT activity induced by our intervention, but only a brief transitory effect of each practice session, which was detectable only by saliva because these samples were obtained shortly after practice sessions. However, even if the effect of the intervention on OT activity is brief, it is likely that frequent repetitions of such surges in OT activity may be beneficial. Additionally, although plasma and salivary OT were correlated, currently very little is known about salivary measures of OT and it is also possible that important distinctions between salivary and plasma OT may exist. For instance, steroid hormones assessed in saliva are "free"; however, when assessed in plasma, both free and protein-bound fractions are included. Given that salivary measures have the potential to be widely

used in research due to the ease in collection and can be done outside a laboratory, thus expanding experimental questions and protocols,[4] additional research is needed to systematically determine any differences. Perhaps the findings from this study may be useful in guiding future research aimed at understanding the utilization of salivary OT as a biomarker.

Overall, these findings complement and build on prior research. The present investigation is consistent with prior research by Grewen et al. (26) in showing that greater social support is linked to higher OT levels in men as well as women. In that study, however, higher OT was linked to lower sympathetic activity only in women (assessed by plasma norepinephrine at rest in the laboratory both before and after couples cuddled for 10 minutes). The present investigation is the first to demonstrate that men as well as women may show decreased sympathetic activity that is linked to increasing OT activity, and that this beneficial effect occurs during real life as well as structured laboratory events. Prior work by Light et al. (46) has also previously shown that higher OT is linked to lower ABP in new mothers, but ours is the first to link it to lower ABP in men.

This study also extends the work of Carter and colleagues (39) in demonstrating the important research potential of taking salivary OT samples at home. Research has shown contrasting effects of OT, as both a buffer of stress and a reaction to it (47). Assessment of OT in humans using plasma may be complicated because of the stress associated with the needle stick to obtain it. Although indwelling catheters can minimize this, the use of salivary OT in this study has the advantage of eliminating any confound of stress associated with obtaining the sample (e.g., less invasive and can be obtained in a more naturalistic setting). Thus, taken together with our data indicating reductions in sympathetic activation, the effect of the intervention on OT reported here can be interpreted more clearly as a reduction rather than exacerbation of stress by increasing warm couple contact. Unfortunately, however, whereas plasma OT was obtained before the intervention, we did not obtain a true pretreatment measure of salivary OT. Likewise, because OT is primarily synthesized in the nervous system, both saliva and plasma OT are indirect measures of central OT activity. In contrast with animal research where OT is most often assessed centrally, OT cannot be directly measured in the human brain. Thus, it is possible that buffering effects of positive social support may take place in the central nervous system. Alternatively, other factors (biological, behavioral, cognitive) may be responsible for both increases in OT and reductions in sympathetic activity.

This study also provides further clarification of one potential way in which to improve the psychophysiological consequences of social relationships. Accumulating evidence suggests that social support is associated with beneficial effects on health outcomes (48,49). More specifically, being married has been associated with lower rates of morbidity and mortality compared with single individuals (2,50) and men seem to benefit more (54). Our data suggest that warm partner contact may be particularly cardioprotective for men. Likewise, prior research has demonstrated a protective role of OT via its influence on anti-inflammatory and autonomic nervous system responses (8,9). Thus, increased support and affection among couples may confer health benefits.

Limitations and Future Directions

Our sample consisted of primarily young and healthy married couples. Likewise, our sample was primarily Caucasian and educated. Therefore, future research will be needed to determine the extent to which these findings may generalize to other populations and other types of social relationships. Likewise, it may be important to test this among both happily married couples and distressed couples. In particular, if healthy, young, well-adjusted couples can show improvement where one might expect a floor effect, then the possibility for improvements among older, less healthy, or distressed couples might be even greater. Alternatively, well-adjusted and/or newly married couples may be more receptive to change and may be more motivated to maintain such practices over the long term. Additional studies which examine factors that may determine likelihood to maintain the practices over longer periods of time and longer follow-up periods are needed. Future research will also be needed to determine potential moderating effects, such as relationship quality, length of marriage, and personality. Future studies may also address whether warm touch is superior to verbal expressions of support and whether combining verbal and warm touch expressions of support is superior to warm touch alone in enhancing OT activity and reducing stress hormones and ABP.

Additionally, our study did not address whether the intervention actually improved the quality of the relationship. Research suggests that distressed couples are at greater health risk (51); thus, it is possible that the health discrepancy between happy and distressed couples may be because happy couples are more affectionate. Likewise, it is possible that the intervention is most effective in a trusting secure (intimate) relationship, where warm contact would be associated with increased perceived affection rather than touch per se. Data on regular massage by a therapist shows inconsistent physiological benefits (52–54), suggesting that relationship factors may be important. One of the notable limitations of the study was that we did not obtain salivary OT before and after treatment, but only during the first and last week of treatment. Because we assessed salivary OT in the evening after couples practiced the "warm touch" techniques, it is unclear whether the obtained difference in OT level represents a transitory increase associated with the recent caring touch or massage, or is a more enduring effect of physical affection and emotional support. Our BP and alpha amylase findings, however, do not have this limitation, and because changes in these measures are consistent with our salivary OT findings, it supports the possibility that all of them reflect a long-term effect. Likewise, the modest but significant increase in OT from week 1 to week

[4]Despite the ease in collection of salivary OT, currently the assay procedures are labor intensive and costly, thus limiting widespread use.

4 of the intervention is inconsistent with a mere transient effect of massage. Nevertheless, research that directly tests these issues is needed.

The present design employed a "monitoring only" control group. The monitoring of physical affection controls for the nonspecific effects of focusing attention on these behaviors. Although all subjects had considerable professional attention during the ABP monitoring and instruction sessions and phone follow-up contacts for salivary and diary monitoring, this control condition does not control for nonspecific effects of additional professional attention and subject expectations of benefits associated with the two assessment sessions. A subsequent investigation with an active control condition, possibly one involving verbal expressions of affection in the absence of warm touch, will be required to clarify whether the observed outcomes are specific to warm touch enhancement support training and home practice.

CONCLUSION

Our findings suggest that supportive behaviors, such as physical affection among couples, may have a beneficial effect on multiple physiological systems associated with stress. The cumulative effect of regular and repeated warm touch was linked to enhanced OT activity, lower stress hormone levels for both husbands and wives, and lower BP among husbands. Although much research exists examining the deleterious effects of negative interactions (e.g., marital conflict, stress), this study addresses the effects of positive couple interactions in both men and women. These findings may help us better understand the protective mechanisms of positive marital interactions in the prevention of stress-related diseases.

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APPENDIX

Appendix A. Details of Oxytocin Extraction and Assay Procedures

Extraction of OT peptide from the same subjects' plasma and saliva samples was performed together in the same batch following these steps, as described in the manual accompanying the OT kit from Assay Designs, Inc., Ann Arbor, Michigan. The first step was to equilibrate a strata-X 33 μm polymeric reversed phase SPE sorbent in a 96-well plate containing 60 mg of sorbent per well (Phenomenex, Torrance, California) by adding 1 ml of MeOH followed by 1 ml of water. The second step was to acidify 0.8 ml of plasma or saliva with 0.4 ml of 1.5% trifluoroacetic acid (TFA) and centrifuge at 6000 *g* for 20 minutes at 4°C. Third, this supernatant was loaded onto the pretreated strata-X plate, and the wells were slowly washed with 1.5 ml of 0.1% TFA. Fourth, the peptide was eluted with 1 ml of 80% acetonitrile; then, the eluant was collected in a polystyrene tube and evaporated to dryness under a N2 stream. Finally, the residue was reconstituted in 250 ul of assay buffer.

The result of this extraction was to concentrate the sample 3.2 times and to reduce matrix interference. Extraction efficiency was determined by spiking samples with a known amount of hormone and extracting with the other samples. Next, OT levels in extracted plasma or saliva were measured in the same batch, using assay kits and protocol obtained in 2006 to 2007 from Assay Designs, Inc. The endogenous OT hormone competes with oxytocin linked to alkaline phosphatase for the oxytocin antibody binding sites. After the overnight incubation at 4°C, the excess reagents were washed away and the bound oxytocin phosphatase was incubated with substrate. After 1 hour, this enzyme reaction (which generates a yellow color) was stopped. The optical density (OD) was read on a Sunrise plate reader (Tecan, Research Triangle Park, North Carolina) at 405 nm. The intensity of the color is inversely proportional to the concentration of oxytocin in the sample. The hormone content (in pg/ml) was determined by plotting the OD of each sample against a standard curve. The kit states that the sensitivity limit of the assay with the current OT antibody (without correcting for the concentration produced by the extraction process) is more than twice as high as with the older antibody at 11.6 pg/ml. With correction for the extraction process as described above, we found that the lower limit of sensitivity was reduced to 2.0 pg/ml. The intra- and interassay variation for this assay is 4.8% and 8%, respectively. Assay Designs reports cross-reactivity for similar neuropeptides found in mammalian sera at <0.001.

Appendix B. Details of Alpha Amylase Assay Procedures

Consistent with prior research (55), concentration of alpha amylase in saliva was measured by an enzyme kinetic method. Saliva was processed on a Genesis RSP8/150 liquid handling system (Tecan, Crailsheim, Germany). First, saliva was diluted 1:625 with double-distilled water by the liquid handling system. Twenty microliters of diluted saliva and standard was then transferred into standard transparent 96-well microplates (Roth, Karlsruhe, Germany). Standard was prepared from Calibrator f.a.s.″ solution (Roche Diagnostics, Mannheim, Germany) with concentrations of 326, 163, 81.5, 40.75, 20.38, 10.19, and 5.01 U/l of alpha amylase, respectively, and bidest water as zero standard. After that, 80 μl of substrate reagent (*a* amylase EPS Sys; Roche Diagnostics, Mannheim, Germany) were pipetted into each well using a multichannel pipette. The microplate containing sample and substrate was then warmed to 37°C by incubation in a waterbath for 90 seconds. Immediately afterward, a first interference measurement was obtained at a wavelength of 405 nm, using a standard enzyme-linked immunosorbent assay (ELISA) reader (Anthos Labtech HT2, Anthos, Krefeld, Germany). The plate was then incubated for another 5 minutes at 37°C in the waterbath, before a second measurement at 405 nm was taken. Increases in absorbance were calculated for unknowns and standards. Increases of absorbance of diluted samples were transformed to

alpha amylase concentrations, using a linear regression calculated for each microplate (Graphpad Prism 4.0c for MacOSX, Graphpad Software, San Diego, California). Inter- and intra-assay variation was <10%. Salivary free cortisol concentrations were measured, using a commercially available chemiluminescence-immuno-assay (CLIA) with high sensitivity of 0.16 ng/μl (IBL, Hamburg, Germany).

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