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A Preliminary Study of the Effects of Repeated Massage on Hypothalamic–Pituitary–Adrenal and Immune Function in Healthy Individuals: A Study of Mechanisms of Action and Dosage

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Abstract

Objectives: This study gathers preliminary data about the biologic effects of repeated Swedish massage therapy compared to a light-touch control condition.
Design: The study design was a 5-week comparison of repeated Swedish massage and light touch on oxytocin (OT), arginine-vasopressin (AVP), adrenal corticotropin hormone (ACTH), cortisol (CORT), circulating phenotypic lymphocyte markers, and mitogen-stimulated cytokine function.
Setting: The setting was an outpatient research unit in an academic medical center.
Participants: The study subjects were medically and psychiatrically healthy young adults.
Intervention: The study comprised 45 minutes of Swedish massage or light touch, using highly specified and identical protocols, either weekly or twice weekly for 5 weeks.
Outcome measures: The outcome measures were mean differences between massage and light touch on OT, AVP, ACTH, CORT, lymphocyte markers, and cytokine levels.
Results: Compared to the touch control condition, weekly Swedish massage stimulated a sustained pattern of increased circulating phenotypic lymphocyte markers and decreased mitogen-stimulated cytokine production, similar to what was previously reported for a single massage session, while having minimal effect on hypothalamic–pituitary–adrenal function. Twice-weekly massage produced a different response pattern with increased OT levels, decreased AVP, and decreased CORT but little effect on circulating lymphocyte phenotypic markers and a slight increase in mitogen-stimulated interferon-γ, tumor necrosis factor-α, interleukin (IL)-1b and IL-2 levels, suggesting increased production of pro-inflammatory cytokines.
Conclusions: There are sustained cumulative biologic actions for the massage and touch interventions that persist for several days or a week, and these differ profoundly depending on the dosage (frequency) of sessions. Confirmatory studies in larger samples are needed.

Introduction

Over 8% of adult Americans had at least one massage session in 2007.[1] Massage is purported to have a wide array of benefits, ranging from being pleasurable to alleviating symptoms of depression, anxiety, back pain, asthma, cancer, and human immunodeficiency virus.[1–14] Despite the popularity and high level of acceptance of massage, meta-analyses report significant reservations about the quality of the majority of studies published in the literature.[4,6,7] The conclusions of these analyses are that massage may reduce pain, stress, depression, anxiety, and cortisol, and enhance some immune parameters, but that more well-controlled studies are needed.[4,6,7,15,16]

There are few investigations attempting to discern the mechanisms of action of massage.[17] When biologic data are reported, the purported biomarkers frequently are laboratory tests that evaluate a particular pathological state rather than measures selected to elucidate the underlying mechanism of action of massage.[3,18–21] There is one publication investigating the mechanism of action of a *single session* of massage in healthy individuals.[22] Swedish massage was associated with

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moderate-to-larger effect size differences in circulating phenotypic lymphocyte markers and mitogen-stimulated cytokine production, small treatment effect size decreases in cortisol levels, and a moderate treatment-effect-size decrease in arginine vasopressin (AVP) levels. There are currently only two published randomized controlled trials of the cumulative biologic effects of *repeated* massage in healthy participants.[23,24] This is important to study because several investigators have reported that the therapeutic effects of massage are evanescent;[4,25,26] thus, repeated massage may have different biologic and psychologic effects than a single session. An added challenge in studying cumulative effects of massage is that they may vary with "dosage" (i.e., the frequency or interval of time between sessions). One may expect that cumulative changes associated with once-weekly massage would increase with more frequent treatments; however, this has not yet been determined.

This study investigated the effects of Swedish massage (the most commonly used form of massage) versus a light touch intervention over 5 weeks on neuroendocrine and immune parameters. The working hypothesis was that repeated massage therapy potentiates the biologic changes identified in this study, comparing a single session of massage therapy versus light touch. The following were postulated: (1) that there would be cumulative effects of 5 weeks of massage versus light touch interventions on biologic measures; (2) that these effects would be sustained beyond the end of the intervention session; and (3) that twice-weekly interventions would enhance the cumulative effects of weekly massage or light touch.

Materials and Methods

Study design

The study was approved by the Cedars-Sinai Medical Center's Institutional Review Board. After providing written informed consent and passing all screening criteria, 53 participants entered the study. Eligible participants were randomized to one of 4 intervention groups, to receive 5 weeks of Swedish massage once a week or twice a week, or a light-touch control condition once a week or twice a week. Forty-five (45) participants (22 male and 23 female) completed the 5-week protocol and so had biologic endpoint data for these analyses. Eight (8) participants dropped out for reasons unrelated to the study intervention, including scheduling conflicts ($n=3$), use of prescription medications to treat injury or illness ($n=4$), and personal disagreement with the therapist ($n=1$). The 8 noncompleters did not differ from study completers on any baseline biologic or psychologic measures. Participants entering the study had to have normal physical examinations and no Axis I psychiatric diagnoses on the structured clinical interview for *Diagnostic & Statistical Manual*, 4th edition (structured clinical interview for DSM-IV).[27] Exclusion criteria included nicotine use, illicit drug use, regular medication use, pregnancy, shift work, dieting, active medical problems, excessive regular use of alcohol (more than two 5-ounce glasses of wine or equivalents/day), or a history of binge drinking (more than 7 drinks/24-hour period) within the last 6 months.

Therapy sessions were performed between 3:00 PM and 7:00 PM by licensed massage therapists for 45 minutes, using a standardized, specified protocol with nonaromatic oils. The light-touch condition followed the same protocol as for Swedish massage except that the therapist used only light touch with the back of the hand. Extensive supervision and quality-control procedures were used to ensure conformance to the protocols. Further details about the protocol and quality assurance procedures can be found elsewhere.[22]

Biologic samples were collected prior to and following the first and last therapy sessions. A heparinized intravenous catheter for blood draws was inserted into the participant's nondominant arm followed by a 30-minute habituation period. Neuroendocrine samples were collected at 5 and 1 minutes prior to the therapy session and at 1, 5, 10, 15, 30, and 60 minutes after the end of the session. Plasma was stored frozen at −80°C until assayed. Immune samples were collected at 1 minute before the therapy session, and at 5 and 60 minutes afterward. Salivary cortisol samples were collected immediately before and 20 minutes after the session.

Biologic assessments

Cortisol and plasma adrenal corticotropin hormone (ACTH) samples were determined by commercial radioimmunoassay (MP Biomedicals, Solon, OH). Oxytocin (OT) and AVP levels were determined by enzyme-linked immunosorbent assays (Assay Designs, Inc., Ann Arbor, MI). Samples were run in duplicate with high and low in-house controls. All samples from each participant were run simultaneously.[22] Measurement of cell surface (CD) markers was performed employing a Becton Dickinson FacScan and BD Immunocytometz reagents, anti-human CD4-FITC, CD8-PE, CD25-PECy5, or CD56-PE, in tandem with appropriate control antibodies. Mitogen-stimulated whole blood culture assays were performed with heparinized whole blood stimulated with 10 μg/mL phytohemagglutinin using methods described elsewhere.[28,29] Unstimulated samples served as controls. Blood cultures were incubated for 48 hours. Supernatants were frozen at −80°C until assayed. Detailed cytokine assay methodology has been presented previously.[22]

Statistical analyses

Analyses were performed based on the 45 participants who completed the 5-week protocol, since biologic measures were obtained prior to and following the first intervention in week 1 and the final (or only) intervention in week 5. Prior to conducting the analyses, the distribution of values on each variable was examined for conformance to a normal distribution and homogeneity of variance. Two (2) different approaches were used to evaluate the cumulative effect of massage versus light touch on biologic measures. The first approach was to compare and contrast the level prior to any treatment in week 1 (baseline level) to the post-treatment level of each variable after the final treatment session in week 5. This is the conventional overall cumulative effect analysis and provides a test of the first hypothesis. In the second approach, mean values were compared and contrasted prior to any intervention (i.e., prior to the first session in week 1) to mean values prior to the final session in week 5. Change in pretreatment levels over the 5 weeks indicate the presence of a sustained effect of repeated massage during the 3–4 day or 1-week interval since the next-to-last intervention session (the test of the second study hypothesis). Both hypotheses

were tested by means of analysis of variance on change, computed as the value of a given biologic measure at the later time point minus the value of that measure at the earlier time point. Change scores were tested to determine whether they were significantly non-zero. Mean change values for all biologic measures are presented separately for the 4 treatment groups. The third study hypothesis was that there would be a dose-dependent enhancement of the previously reported findings of massage versus touch changes during a single intervention session,[22] such that the cumulative changes would be greater for the twice-a-week dose group than the once-a-week group. This was analyzed by computing a Cohen's d[30] treatment effect size for massage versus touch separately for twice-a-week and once-a-week dose groups, as well as a dose effect (twice-a-week versus once a week) separately within massage and touch groups. Because of the small number of participants in the randomized treatment groups, effect size is more meaningful than statistical significance.[31]

Where multiple pretreatment measurements were collected, the average value was used in computing change. In keeping with *a priori* hypotheses concerning the direction of changes in neuroendocrine variables, post-treatment values were based on the *maximum* of the six post-treatment values (OT) or *minimum* of the six post-treatment values (AVP, ACTH, and plasma cortisol). The 60-minute postintervention time point was used to evaluate immune parameters.[22]

Results

There were no differences in demographics (Table 1) or in baseline biologic values (Table 2) across the 4 randomized treatment groups, as determined by analysis of variance or χ^2 tests.

Overall cumulative change over 5 weeks of treatment

Table 3 presents the overall cumulative neuroendocrine and immune effects of 5 weeks of massage versus light touch. In this approach, baseline measures prior to any intervention at week 1 are subtracted from postintervention measures obtained after the final treatment session in week 5.

Once-a-week treatment

Endocrine measures. Once-a-week massage caused a moderately large treatment-effect size decrease of −0.56 for ACTH and small effect-size differences for OT (-0.14), AVP (0.06), plasma cortisol (-0.07), and salivary cortisol (-0.26).

Lymphocytes. Mean levels of total lymphocytes and all four lymphocyte cell types increased substantially with weekly massage but decreased substantially with weekly touch, resulting in large treatment-effect sizes for total lymphocytes (1.27), CD4+ cells (1.10), CD8+ cells (1.15), CD25+ cells (0.77), and CD56+ cells (1.09).

Cytokines. Once-a-week massage was associated with large treatment-effect sizes for interleukin (IL)-5 (-1.02), IL-10 (-0.80), and IL-13 (-1.24) due to decreases in mean levels associated with repeated massage, while levels of these measures increased for participants treated with touch. A mean decrease for massage but increase for touch was found, and resulted in moderate treatment effect sizes, for IL-2 (-0.54) and tumor necrosis factor (TNF)-α (-0.57). IL-4 had an effect size in the moderate range (0.48) driven by a decrease in the touch group, and stable levels for massage. IL-1b increased less for massage than for touch (-0.33). Treatment-effect sizes were negligible for IFN-γ (-0.06) and IL-6 (-0.09).

Twice-a-week treatment

Endocrine measures. Massage increased OT (0.50) and decreased salivary cortisol (-0.67) more than touch. Massage decreased AVP more than for touch (-0.32), while treatment effects for ACTH and plasma cortisol were negligible (-0.09).

Lymphocytes. CD56+ cells increased more for massage than touch (0.41), while mean numbers of CD4+ cells and CD25+ cells, and total lymphocytes, increased less for massage than for touch (-0.33, -0.36, -0.20, respectively). Mean numbers of CD8+ cells increased about the same for both groups (0.03).

Cytokines. There was a large treatment effect difference for TNF-α (0.68), due to increased TNF-α levels for massage and decreased levels for touch. Treatment-effect sizes were in the small range for IL-1b (0.36) due to a larger increase for massage group, and for IL-6 (-0.33) due to a smaller increase for massage group. Treatment-effect sizes were small for IFN-γ (0.26), IL-2 (0.14), IL-4 (0.17), IL-5 (-0.03), IL-10 (-0.20), and IL-13 (-0.27).

Table 1. Demographic Characteristics of Study Participants

	Study participants (N = 45)	
Age, mean (SD)	31.3	(6.4)
(range)	(19–44)	
Female, *N* (%)	23	(51.1)
Ethnicity, *N* (%)		
White	22	(48.9)
Asian	9	(20.0)
Hispanic	8	(17.8)
Afr. American	5	(11.1)
Other	1	(2.2)

SD, standard deviation.

Change in Pretreatment Measures Over 5 Weeks of Treatment

This analysis reports the change in biologic measures computed by subtracting values prior to initiation of any treatment intervention at week 1, from pre-intervention measures before the final session at week 5. Thus, Table 4 indicates whether the cumulative changes are sustained between intervention sessions (intervals of 7–8 days for weekly and 3–4 days for twice weekly).

Once-a-week treatment

Endocrine measures. Repeated massage was associated with small positive effect-size differences for change in levels of OT (0.05), AVP (0.24), and salivary cortisol levels (0.06), and small negative effect differences in ACTH (-0.23) and plasma cortisol (-0.21) levels.

Table 2. Biologic Measures at Baseline (Prior to First Intervention)

	1x/wk						*2x/wk*					
	Massage			*Touch*			*Massage*			*Touch*		
Variable	N	*Mean*	*SD*	N	*Mean*	*SD*	N	*Mean*	*SD*	N	*Mean*	*SD*
Endocrine measures												
OT[a,b]	10	180.4	89.6	12	179.3	160.8	10	180.9	79.7	9	273.7	173.7
AVP[a,b]	9	63.53	42.51	12	76.47	67.87	8	69.91	48.06	9	53.77	33.91
ACTH[a,b]	6	64.43	20.65	7	57.66	16.74	5	62.07	10.80	3	79.02	9.94
Plasma cortisol[a,c]	11	26.28	7.41	12	26.34	17.18	13	28.43	16.46	9	29.34	23.08
Salivary cortisol[c]	10	0.613	0.337	11	0.457	0.316	13	0.629	0.438	8	0.521	0.241
Lymphocyte subset counts[d]												
Total lymphocytes	10	1,801,000	623,760	11	2,249,091	777,399	12	2,200,583	1,181,110	9	1,768,889	894,350
CD4	10	724,700	265,321	10	854,300	292,234	11	1,036,000	590,346	9	851,111	529,919
CD8	10	535,100	278,375	10	617,600	301,879	11	607,364	298,152	9	477,889	213,737
CD25	10	668,700	311,511	10	671,200	311,313	11	719,455	280,984	9	668,222	632,808
CD56	10	199,580	78,079	10	395,400	278,000	12	254,317	152,689	9	275,078	143,030
In vitro cytokine levels[e]												
IFN-γ	6	16.83	16.81	7	57.22	58.12	12	40.32	62.57	8	31.09	32.81
IL-1β	6	1.06	0.76	7	2.38	3.54	12	1.25	1.56	8	0.89	1.13
IL-2	5	0.185	0.163	7	0.278	0.182	11	0.453	0.693	7	0.214	0.223
IL-4	6	0.311	0.103	8	1.056	2.379	11	0.383	0.421	6	0.355	0.286
IL-5	6	0.690	0.824	8	0.790	0.930	12	0.926	1.814	5	0.993	1.049
IL-6	4	31.31	15.19	4	18.92	14.40	7	18.06	16.25	6	16.34	17.15
IL-10	6	31.88	48.30	7	13.40	16.07	11	37.43	96.84	7	7.02	12.05
IL-13	6	3.98	6.34	7	2.59	3.18	11	10.62	22.99	7	2.98	5.81
TNF-α	8	5.26	4.90	8	8.67	12.64	12	5.56	6.86	8	5.39	10.43

No significant differences were observed among the 4 randomized groups.
[a]Values are the average between two pretreatment samples collected.
[b]In pg/mL.
[c]In μg/dL.
[d]In cells/mL.
[e]In pg/10^4 lymphocytes.
SD, standard deviation; OT, oxytocin; AVP, arginine vasopressin; ACTH, adrenal corticotropin hormone; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

Lymphocytes. Massage was associated with increased mean numbers of total lymphocytes (1.21), CD4+ cells (0.92), CD8+ cells (1.12), CD25+ cells (0.46), and CD56+ cells (0.87), while there were decreases in mean levels of all of these measures for the touch group.

Cytokines. Change in levels of mitogen-stimulated cytokine production is characterized by large effect sizes (-0.62 to -1.19) for IL-2, IL-5, IL-10, and IL-13 due to decreases in the massage group and increases in these measures for the touch group. There were moderate effect sizes for IFN-γ (0.33) and IL-4 (0.37) due to mean levels decreasing less for massage than for touch, as well as for IL-1b (-0.42) due to a smaller increase for massage than for touch, and TNF-α (-0.31) due to a larger decrease for massage than for touch. There was a very small effect size difference in IL-6 levels.

Twice-a-week treatment

Endocrine measures. Twice-a-week massage versus light touch has a distinctly different pattern of neuroendocrine effects than once-weekly treatment. AVP decreased with massage but increased with touch, resulting in a large treatment effect size (-1.14). There were large effect sizes for OT (0.92) and ACTH (0.95), driven by decreases for the touch group, while the massage group had a stable mean OT level and a smaller decrease in ACTH levels. Mean levels of salivary cortisol (-0.42) and plasma cortisol (-0.22) increased over 5 weeks with touch, but decreased (salivary) or remained about the same (plasma) with massage.

Lymphocytes. There was a moderate treatment-effect size (0.66) for CD56+ cells due to decrease in cells for the touch group compared to an increase for the massage group. There were moderate treatment effect sizes for total lymphocytes (-0.38), CD4+ cells (-0.47), and CD25+ cells (-0.35) due to increases for the touch group while levels decreased on these measures for the massage group. Levels of CD8+ cells (-0.05) decreased about the same for both groups.

Cytokines. The positive effect size for TNF-α (0.68) was due to an increase in levels for the massage group and a decrease in levels for the touch group, and for IL-5 (0.54), was due to a decrease in levels for the touch group but a stable level for the massage group. There were moderate effect-size differences for IFN-γ (0.36), IL-1b (0.37), and IL-2 (0.32) due to larger increases in mean levels associated with the massage group, compared to a smaller increase for the touch group on IFN-γ and stable mean levels on IL-1b and IL-2.

Table 3. Cumulative Change Between Baseline (Pretreatment) Levels at First Session and Post-treatment Levels After Final Session of Therapy

	1x/wk						2x/wk						Treatment effect size[a]		Dose effect size[b]	
	Massage			Touch			Massage			Touch						
Variable	*Mean*	*SD*		*Mean*	*SD*		*Mean*	*SD*		*Mean*	*SD*		*1x*	*2x*	*Mass.*	*Touch*
Endocrine measures																
OT[c]	16.7	44.0		22.9	46.5		27.6	35.5	*	8.1	42.0		−0.14	0.50	0.28	−0.33
AVP[c]	−15.03	16.85	*	−16.45	26.35		−10.94	22.86		−5.21	12.76		0.06	−0.32	0.21	0.51
ACTH[c]	−13.93	4.48	*	−9.86	8.88	*	−14.73	16.54		−13.52	6.49		−0.56	−0.09	−0.07	−0.45
Plasma cortisol[d]	−12.55	7.96	*	−11.96	8.99	*	−8.31	9.51	*	−7.60	4.20	*	−0.07	−0.09	0.48	0.58
Salivary cortisol[d]	−0.265	0.275	*	−0.194	0.291		−0.276	0.337	*	−0.064	0.236		−0.26	−0.67	−0.04	0.48
Lymphocyte subset counts[e]																
Total lymphocytes	716,000	432,286	*	−206,364	667,717		182,750	748,594		341,250	928,539		1.27	−0.20	−0.80	0.67
CD4	292,400	207,087	*	−86,100	359,759		14,455	344,471		160,250	572,441		1.10	−0.33	−0.88	0.53
CD8	230,000	241,410	*	−72,400	191,147		75,091	224,935		68,375	218,601		1.15	0.03	−0.64	0.67
CD25	162,100	189,023	*	−43,778	309,379		32,700	145,960		161,125	517,070		0.77	−0.36	−0.73	0.49
CD56	83,480	80,403	*	−57,410	133,018		73,767	89,264	*	34,075	110,237		1.09	0.41	−0.12	0.71
In vitro cytokine levels[f]																
IFN-γ	−3.86	10.70		−0.95	72.86		51.57	76.48	*	31.09	89.99		−0.06	0.26	0.82	0.40
IL-1β	0.32	0.62		0.84	2.25		4.44	13.76		0.52	0.95		−0.33	0.36	0.37	−0.20
IL-2	−0.055	0.114		0.099	0.375		0.179	0.701		0.104	0.119		−0.54	0.14	0.40	0.02
IL-4	−0.002	0.103		−0.683	1.936		0.096	0.315		0.042	0.380		0.48	0.17	0.38	0.50
IL-5	−0.333	0.519		0.322	0.608		0.083	1.394		0.118	1.306		−1.02	−0.03	0.35	−0.22
IL-6	−2.98	35.02		−0.75	16.66		6.04	9.55		9.56	12.91		−0.09	−0.33	0.43	0.70
IL-10	−13.64	24.77		40.83	88.70		−8.23	68.46		2.11	3.14		−0.80	−0.20	0.10	−0.64
IL-13	−1.91	3.53		2.56	2.09	*	−3.73	15.11		−0.56	3.53		−1.24	−0.27	−0.15	−0.96
TNF-α	−2.51	4.51		1.53	9.56		6.41	12.65		−1.04	4.92		−0.57	0.68	0.81	−0.36

Change is computed as the post-treatment values at the final visit minus minus baseline levels prior to the first visit (Table 2).
[a]Treatment-effect sizes are computed for the effect of massage contrasted with touch, within once-a-week or twice-a-week dose groups.
[b]Dose-effect sizes are computed for the effect of twice-a-week contrasted with once-a-week sessions, within massage or touch treatment groups.
[c]In pg/mL.
[d]In μg/dL.
[e]In cells/mL.
[f]In pg/10^4 lymphocytes.
*Change value significantly nonzero, $p < 0.05$.
SD, standard deviation; OT, oxytocin; AVP, arginine vasopressin; ACTH, adrenal corticotropin hormone; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

Table 4. Cumulative Change Between Pretreatment Levels at First and Final Session of Therapy

	1x/wk					2x/wk								
	Massage		Touch			Massage		Touch			Treatment effect size[a]		Dose effect size[b]	
Variable	*Mean*	*SD*	*Mean*	*SD*		*Mean*	*SD*	*Mean*	*SD*		*1x*	*2x*	*Mass.*	*Touch*
Endocrine measures														
OT[c]	−11.2	39.9	−13.9	63.6		0.9	28.1	−24.7	21.9	*	0.05	0.92	0.35	−0.22
AVP[c]	−3.99	10.17	−7.79	18.96		−7.13	8.65	1.82	4.00		0.24	−1.14	−0.34	0.64
ACTH[c]	0.15	8.75	2.06	8.51		−2.47	11.08	−14.88	14.28		−0.23	0.95	−0.28	−1.34
Plasma cortisol[d]	−2.96	9.60	−1.25	7.10		0.06	11.84	2.11	4.49		−0.21	−0.22	0.28	0.54
Salivary cortisol[d]	−0.066	0.383	−0.090	0.403		−0.106	0.411	0.089	0.556		0.06	−0.42	−0.10	0.38
Lymphocyte subset counts[e]														
Total lymphocytes	438,100	522,278	*	−267,273	416,103		−193,083	559,928	30,667	636,666		1.21	−0.38	−1.02	0.56
CD4	203,600	278,723	*	−73,300	267,206		−127,091	255,990	9,333	326,238		0.92	−0.47	−1.07	0.28
CD8	174,610	262,462		−107,300	144,760	*	−34,000	182,542	−26,111	170,851		1.12	−0.05	−0.86	0.51
CD25	69,600	210,079		−51,000	305,815		−45,273	215,767	43,222	293,124		0.46	−0.35	−0.53	0.32
CD56	28,000	77,957		−60,330	105,918		26,433	121,609	−46,878	83,851		0.87	0.66	−0.02	0.14
In vitro cytokine levels[f]														
IFN-γ	−1.58	12.04	−11.94	42.81		31.95	56.44	10.22	69.32		0.33	0.36	0.69	0.38
IL-1β	0.19	1.02	1.01	2.55		0.87	3.01	−0.04	1.25		−0.42	0.37	0.27	−0.54
IL-2	−0.075	0.145	0.072	0.278		0.145	0.592	−0.011	0.260		−0.62	0.32	0.44	−0.31
IL-4	−0.008	0.186	−0.396	1.385		0.006	0.258	−0.047	0.232		0.37	0.22	0.06	0.34
IL-5	−0.345	0.546	0.071	0.363		−0.035	0.861	−0.481	0.722		−0.87	0.54	0.40	−0.96
IL-6	1.80	24.29	0.16	31.32		1.33	12.00	3.36	10.23		0.06	−0.19	−0.03	0.16
IL-10	−14.32	23.35	21.35	25.41		−8.83	63.34	2.42	11.12		−1.19	−0.23	0.11	−0.89
IL-13	−1.72	2.62	4.33	5.35		−2.43	12.60	−0.32	0.98		−1.16	−0.22	−0.07	−1.05
TNF-α	−2.17	4.19	−0.37	7.16		3.46	7.84	−1.89	7.19		−0.31	0.68	0.80	−0.22

Change is computed as the pretreatment values at the final visit minus baseline levels prior to the first visit (Table 2).
[a]Treatment-effect sizes are computed for the effect massage contrasted with touch, within once-a-week or twice-a-week dose groups.
[b]Dose-effect sizes are computed for the effect of twice-a-week contrasted with once-a-week sessions, within massage or touch treatment groups.
[c]In pg/mL.
[d]In μg/dL.
[e]In cells/mL.
[f]In pg/10^4 lymphocytes.
*Change value significantly nonzero, $p < 0.05$.
SD, standard deviation; OT, oxytocin; AVP, arginine vasopressin; ACTH, adrenal corticotropin hormone; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

Effects of Intervention Frequency ("Dose") Within Massage or Light Touch

There were no large effect-size differences for neuroendocrine measures between once-weekly and twice-weekly massage sessions by either of the analytic approaches. Twice-weekly touch, on the other hand, appears to have had a consistently greater moderating effect on all stress-related hormones than once-weekly touch (Table 3). The dosage effect was particularly striking for change in pretreatment levels of ACTH (Table 4).

The frequency of the interventions showed an *opposite* effect for massage versus light touch on cumulative measures of circulating lymphocyte measures. Total lymphocyte counts, CD4+ cells, CD8+ cells, and CD25+ cells all increased with once-weekly sessions (Table 3). Mean pretreatment levels at the last visit for these four measures decreased with twice-weekly massage (Table 4). In contrast, the touch intervention caused decreases in mean levels on all lymphocyte measures with once-weekly sessions, but increases with the twice-weekly touch (Table 3) for three of the five lymphocyte measures (Table 4).

Massage was associated with small decreases in IFN-γ and TNF-α with once-a-week sessions, but large increases in these two cytokines with twice-a-week sessions. This was consistent across both analytic approaches (Tables 3 and 4). Within the touch groups, the mean level of IL-13 increased with once-weekly sessions but decreased with twice-weekly intervention (Tables 3 and 4).

Conclusions

The data suggest that massage therapy has cumulative and sustained biologic effects over the course of 5 weeks. Results of the first approach, comparing baseline biologic measures to postintervention data after the final session in week 5, indicates that there are cumulative biologic effects of massage and light touch, and that these differ according to the frequency of interventions. Once-a-week massage demonstrated patterns of change in circulating lymphocyte markers and cytokine expression similar to what was observed after a single massage session.[22] Repeated weekly massage potentiates the effects of the immune changes that were identified after a single session of massage, but has minimal effect on neuroendocrine function. By contrast, twice-weekly massage potentiates neuroendocrine changes consistent with the initial hypothesis that the beneficial effects of massage therapy might be mediated through OT and AVP. In contradistinction to the single-session study and the weekly massage findings, immune system changes found for twice-weekly massage included a slight increase in production of pro-inflammatory and TH-1 cytokines and a decrease in most circulating phenotypic lymphocyte markers.

Results from this study's second analytic approach suggest there may be *sustained* cumulative biologic effects caused by the massage and light touch interventions. The once-a-week and twice-a-week intervention groups show biologically distinct effects that are not merely an additive effect caused by increasing the frequency of interventions. The twice-a-week massage group demonstrated greater changes in OT, AVP, ACTH, and cortisol than the twice-a-week touch group: changes that were sustained over a 3–4-day period between treatments. Once-a-week massage and once-a-week touch differed in terms of circulating leukocyte markers and mitogen-stimulated cytokine responses. Similar to a single session,[22] repeated weekly massage caused increases in pretreatment numbers of all lymphocyte subsets, compared to decreases for weekly touch: changes that persisted for 7 or 8 days between the last two sessions. Twice-weekly massage increased mean pretreatment levels of CD56+ cells, but decreased all other circulating phenotypic markers. Changes in pretreatment levels of mitogen-stimulated cytokine expression in the once-a-week group are similar to the authors' previous report[22] with sustained decreases in many pro-inflammatory and TH-2 cytokines. These treatment differences were not seen in the twice-weekly intervention groups. (It is important to note that the weekly massage sessions were separated by 7–8 days, while the twice-weekly sessions were separated by 3–4 days; thus, some of the differences observed may represent differences in length of time between sessions.) As a whole, the current findings suggest that (1) there are cumulative biologic effects of repeated massage versus light touch, (2) some of these effects are sustained for several days or a week, and (3) these effects are different depending on the "dosage" of the interventions.

Although these findings require replication, they suggest that the "dosage" of massage may result in profoundly different biologic actions, and one might want to adjust the dosage based on the effect desired. This observation may explain why there are problems replicating biologic and psychologic findings in the massage literature: studies vary greatly in intervention frequency, length, and type.[4,7,26] The authors believe that further systematic studies in healthy individuals are needed to replicate and extend the current findings, in addition to studying the therapeutic value of massage for specific populations such as stressed or immune-system-compromised individuals. It is believed that understanding of the mechanisms of action underlying the effects of massage and light touch in *healthy* individuals, including the effect of different frequency (dosage) regimens on different biologic systems, will help to guide the design of studies aimed at having specific therapeutic effects for targeted populations.

Another intriguing finding of this study is that the light touch condition, involving gentle, systematic, and comprehensive stroking of an individual for 45 minutes, does have biologic activity.[25,32] Further research is needed to identify the specific biologic effects associated with different types of touch and relaxation interventions. A recent quantitative review by Moyer et al.[33] points out that the 19 published randomized controlled clinical trial reports that provide data on between-groups effects of massage on one biologic outcome, cortisol, differ greatly in terms of treatment-effect size. This is likely to be due to differences in study populations, the nature of the comparison treatment(s), and the duration, frequency, and total number of sessions. Furthermore, the two previously published reports of multiple massage sessions in healthy individuals[23,24] show little cumulative influence on salivary cortisol (treatment effect sizes of 0.11 and 0.18). Whether this raises a question about cortisol as an underlying mechanism of action for demonstrated benefits of massage clearly requires further systematic and well-controlled research. Using the same intervention schedule (twice weekly for 5 weeks), the present study showed a

modestly greater reduction in salivary cortisol (but not plasma cortisol) associated with twice-a-week (but not once-a-week) sessions of massage versus light touch, with treatment-effect sizes 0.67 for the cumulative effect and 0.42 for its persistence over 3–4 days.

There are limitations of this study, such as the small sample size of the groups. Small sample sizes can lead to an overestimate of effect sizes and thus, the data must be considered within the context of this caveat.[31,34] A second concern in studies where one is attempting to measure a decrease in hormones normally associated with a stress response in unstressed, normal volunteers is that there may be a floor effect, resulting in underestimation of the degree of benefit that stressed or ill individuals may receive from the intervention. Yet, in order to appreciate the impact of the intervention itself on human physiology, it is important to study healthy participants. Another limitation is that this study only isolates the impact of the *effleurage*, *petrissage*, kneading, *tapotement*, and thumb friction employed in Swedish massage. Participants who underwent light touch received whatever benefit one receives from repeated systematic light touch, disrobing, and spending 45 minutes relaxing on the massage table. Different control conditions less similar to Swedish massage might yield more profound biologic findings. Studying the effects of massage compared to the light touch active control condition provides information about the specific effects of deep tissue manipulation, which is a distinguishing characteristic of Swedish massage. Ideally, one could systematically "deconstruct" the aspects of the intervention responsible for specific biologic effects by studying the effects of massage compared to a series of conditions with decreasing similarity such as light touch (which differs only in the nature of the manipulation), and lying on a table under a sheet after disrobing (a relaxation condition that is similar in every respect but involves no manipulation). Another possible concern is that this study did not report measures of sympathetic/parasympathetic tone. Heart rate variability was measured, but no differences were found between the groups. This is not surprising, since a young, healthy sample was studied. The study did not control for menses, but the phase of the menstrual cycle was recorded for female participants and no differences were observed.

In conclusion, the pilot data suggest that there are sustained cumulative biologic effects of repeated massage and light touch on neuroendocrine and immune parameters in healthy volunteers, but these differ by dosage. Weekly massage increased circulating phenotypic lymphocyte markers and decreased mitogen-stimulated cytokine production with a minimal effect on HPA function. Twice-weekly massage appears to potentiate neuroendocrine differences. These findings suggest that further investigation of "dosage," as well as length of treatment and deconstructing the massage technique, are needed.

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Dr. Rapaport is on the Scientific Advisory Board of the Depression and Bipolar Disorder Alternative Treatment Foundation, a journal editor for the American Psychiatric Association, and an unpaid consultant to PAX, Inc. Dr. Schettler provides statistical consulting services to Brain Cell, Inc.; Methylation Sciences; and Novartis BioVentures. Ms. Bresee has no financial conflicts of interest.

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