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A Preliminary Study of the Effects of a Single Session of Swedish Massage on Hypothalamic–Pituitary–Adrenal and Immune Function in Normal Individuals

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Abstract

Objectives: Massage therapy is a multi–billion dollar industry in the United States with 8.7% of adults receiving at least one massage within the last year; yet, little is known about the physiologic effects of a single session of massage in healthy individuals. The purpose of this study was to determine effects of a single session of Swedish massage on neuroendocrine and immune function. It was hypothesized that Swedish Massage Therapy would increase oxytocin (OT) levels, which would lead to a decrease in hypothalamic–pituitary–adrenal (HPA) activity and enhanced immune function.
Design: The study design was a head-to-head, single-session comparison of Swedish Massage Therapy with a light touch control condition. Serial measurements were performed to determine OT, arginine-vasopressin (AVP), adrenal corticotropin hormone (ACTH), cortisol (CORT), circulating phenotypic lymphocytes markers, and mitogen-stimulated cytokine production.
Setting: This research was conducted in an outpatient research unit in an academic medical center.
Subjects: Medically and psychiatrically healthy adults, 18–45 years old, participated in this study.
Intervention: The intervention tested was 45 minutes of Swedish Massage Therapy versus a light touch control condition, using highly specified and identical protocols.
Outcome measures: The standardized mean difference was calculated between Swedish Massage Therapy versus light touch on pre- to postintervention change in levels of OT, AVP, ACTH, CORT, lymphocyte markers, and cytokine levels.
Results: Compared to light touch, Swedish Massage Therapy caused a large effect size decrease in AVP, and a small effect size decrease in CORT, but these findings were not mediated by OT. Massage increased the number of circulating lymphocytes, CD 25+ lymphocytes, CD 56+ lymphocytes, CD4 + lymphocytes, and CD8+ lymphocytes (effect sizes from 0.14 to 0.43). Mitogen-stimulated levels of interleukin (IL)–1ß, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, and IFN-γ decreased for subjects receiving Swedish Massage Therapy versus light touch (effect sizes from -0.22 to -0.63). Swedish Massage Therapy decreased IL-4, IL-5, IL-10, and IL-13 levels relative to baseline measures.
Conclusions: Preliminary data suggest that a single session of Swedish Massage Therapy produces measurable biologic effects. If replicated, these findings may have implications for managing inflammatory and autoimmune conditions.

Introduction

The December 6, 2008, National Health Statistics Report indicates that nearly 4 of 10 adults and approximately 1 of 9 children had used some form of complementary and alternative medicine (CAM) in the past year.[1] One of the most widely accepted manual CAM therapies is massage therapy, which has become a multi–billion dollar industry in the United States, with 8.3% of adults receiving at least one massage treatment in the year 2007.[1] Individuals seek massage therapy as a treatment for a myriad of conditions ranging from muscle aches, back pain, headaches, and insomnia, to

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psychologic stress, anxiety, and depression.[1–5] Despite the popularity of massage therapy, little is known about its physiologic actions.[1] Recent reviews suggest that massage therapy may have short-term effects such as decreasing pain and increasing qualify of life (QoL) in patients who have cancer.[6, 7] Massage therapy stimulates weight gain and may decrease length of stay for preterm infants in neonatal intensive care visits as well as reducing prematurity.[4,8–11] There are also reports of small studies, about a variety of different syndromes, indicating that massage therapy may cause a short-term decrease in urine, salivary, and serum cortisol levels.[12–16] Massage therapy has also been demonstrated to improve immune function with an increase in the number of circulating natural killer (NK) cells and circulating lymphocytes.[17–22] Although these studies suggest that massage therapy may benefit certain individuals, recent meta-analyses and reviews conclude that methodological problems in studies of massage severely limit their ability to generate scientifically valid and generalizable conclusions.[4,6,23,24] There is a need for well-controlled, rigorous research trials in healthy individuals to determine the acute biologic effects of this widely accepted therapy. The data presented in this article comprise an important first step in that process.

Under the aegis of a National Center for Complementary and Alternative Medicine (NCCAM) exploratory grant, the physiologic effects of a single session of Swedish Massage Therapy versus a light touch control condition were studied. Based on previously published work and the current authors' unpublished pilot preclinical data, it was hypothesized that the physiologic and psychologic actions of massage therapy are mediated by oxytocin (OT).[25–29] OT has been shown to have a blunting effect on the hypothalamic–pituitary–adrenal (HPA) axis, decreasing cortisol (CORT) and improving the stress response.[30–34] The working hypothesis was that Swedish Massage Therapy would cause an increase in OT, a decrease in arginine vasopressin (AVP), a decrease in HPA axis activity ([adrenal corticotropin hormone ([ACTH] and CORT), demargination of leukocytes from the periphery into circulation, and enhanced immune function as measured by an *in vitro* cytokine assay. This study was designed to identify the magnitude of the treatment effect size for Swedish Massage Therapy versus light touch on changes in these biologic measures, and to generate data needed to design larger confirmatory studies.

Materials and Methods

Study design

The study was approved by the Cedars-Sinai Medical Center's (Los Angeles, CA) institutional review board. After providing written informed consent, 53 study participants (24 male and 29 female) were randomized to receive either Swedish Massage Therapy, a deep tissue massage, ($n = 29$), or a light touch protocol, which served as a control condition, ($n = 24$). This study was conducted as part of a feasibility trial designed to compare both the acute effects of a single session of massage or light touch, as well as the longer-term effects of massage therapy. Subjects were medically healthy and free of any current or past Axis I psychopathology as determined by physical examination and the structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (*DSM-IV*) Axis I disorders (SCID).[35] Exclusion criteria included current nicotine use, illicit drug use, regular medication use, pregnancy, shift work, current dieting, active medical problems, excessive regular use of alcohol (more than two 5-oz glasses of wine or equivalents/day), or a history of binge drinking (more than 7 drinks/24-hour period) within the last 6 months. Women using hormonal contraceptives were not excluded. Subjects were asked to refrain from any nonprescription medication use for at least 48 hours and to eat a light meal within 3–4 hours prior to their appointment.

Therapy sessions were scheduled between 3:00 PM and 7:00 PM. Upon arrival, each subject changed into a gown and a heparinized intravenous (IV) catheter for blood draws was inserted into the nondominant arm. Subjects were then asked to rest quietly for 30 minutes prior to the therapy session to become habituated to the catheter.

Both interventions were performed by licensed massage therapists for 45 minutes, using a standardized protocol with nonaromatic massage oils. The room was lighted dimly and a sound machine was used to mask unwanted noises with ocean sounds. Each subject began the session while draped with a sheet over the body and in a prone position on a massage table while the therapist worked slowly down the body from the shoulders to the feet. The subject then turned over to the supine position, and the therapist repeated the process from the feet back up to the shoulders. Swedish Massage Therapy techniques included effleurage, petrissage, kneading, tapotement, and thumb friction. The control treatment was performed by the same therapists with an identical protocol, except that the therapist used only a light touch with the back of the hand. Sessions were audiotaped for quality control. Neither the massage therapists nor the subjects were aware of the overarching hypothesis for this study. Massage therapists were trained in both the massage and light touch protocols, and the sessions were monitored via audiotapes and postsession interviews with the subjects about the intervention sessions. The massage therapists were supervised by the head of the Cedars-Sinai Medical Center's integrative medicine program, an individual who has expertise in Swedish Massage Therapy.

For the assessment of HPA axis activity, blood 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 45-minute session. Plasma was collected and then stored frozen at $-80^{\circ}C$ until assayed. To measure immune function, separate blood samples were also collected at 1 minute before the therapy session and 5 and 60 minutes afterward. Blood was collected and kept at room temperature, and processed within 2 hours of collection. Salivary CORT samples were collected immediately before and 20 minutes after the therapy session. Self-reported psychologic assessment forms were filled out by the study subjects, 15 minutes before and 15 minutes after the therapy session.

Biologic assessments

Plasma and salivary CORT as well as plasma ACTH levels were determined by commercial radioimmunoassay (MP Biomedicals, Solon, OH). Plasma levels of OT and AVP were determined by enzyme-linked immunosorbent assays (ELISAs; Assay Designs, Inc., Ann Arbor, MI). All samples were run in duplicate for all assays with high and low in-house

controls. All samples from each subject were run together on the same assay for each HPA axis biomarker.

Measurement of cell surface (CD) markers was performed via flow cytometry with reagents from Becton Dickinson Immunocytometry Systems (San Jose, CA) per the manufacturer's directions using antihuman CD4-FITC, CD8-PE, CD25-PECy5, or CD56-PE, in tandem with appropriate control antibodies. Samples were tested, using standard flow cytometry techniques on a Becton Dickinson FacScan (BD Biosciences, San Jose, CA).

For cytokine assessment, mitogen-stimulated whole-blood culture assays were performed with heparinized whole blood stimulated with 10 μg/mL of phytohaemagglutinin (PHA), using methods as described elsewhere.[36,37] Unstimulated samples (no PHA added) served as controls. Blood cultures were incubated for 48 hours. Supernatants were recovered and kept frozen at -80°C until further analysis could be performed for cytokine determination using the FAST Quant human TH1/TH2 cytokine protein microarray (Whatman, Piscataway, NJ), according to the manufacturer's recommendations. IL-1ß, IL-2, IL-4, IL-6, IL-10, IFN-γ, and TNF-α levels were determined with analysis by Whatman slide scanning services. Appropriate controls were included in each assay to correct for interassay variation. Measured pg/mL cytokine concentrations were converted to pg/10^4 lymphocytes to correct for changes in lymphocyte numbers in each whole-blood sample assayed. (See Appendix 1 for greater details about assay methodology.)

Psychologic assessments

Psychologic assessments included 3 self-report scales: the Quick Inventory of Depressive Symptoms Self Report form (QIDS-SR)[38]; the Profile of Mood States (POMS)[39]; and the State-Trait Anxiety Inventory (STAI).[40] All are self-report scales. The QIDS-SR is a 16-item scale that assesses the severity of depression over the past 7 days. The POMS is a 65-item scale to measure six mood states—tension, anger, vigor, fatigue, and confusion—over the past 7 days. The STAI is a 40-item scale that measures both state (at the moment) and trait (in general) levels of anxiety.

Statistical analysis

The acute effects of Swedish Massage Therapy versus light touch were evaluated for each biologic and psychologic variable based on subjects who had available data for both pre- and post-treatment timepoints. Prior to conducting the analysis, the distribution of values on each variable was examined for conformance to a normal distribution. Data not normally distributed was log transformed prior to analysis. Changes from pre- to post-intervention were analyzed as the changes in the log-transformed values when appropriate.

In keeping with *a priori* hypotheses concerning the direction of changes in HPA axis variables that would be associated with massage, change for these variables was based on the *maximum* of the 6 post-treatment values (OT) or *minimum* of the 6 post-treatment values (AVP, ACTH, and plasma CORT) minus the average of the 2 pretreatment values. Given that the current authors were not aware of any study of the timing of the effect of massage on HPA axis variables, this study also examined the percentage of subjects in each group who experienced their maximum/minimum values at each of the 6 post-treatment blood samplings. Change in salivary CORT was based on the difference between the single pretreatment versus post-treatment measures. Given that the direction of change for those variables was not guided by *a priori* hypotheses in this exploratory study, absolute change for lymphocytes and cytokines was computed based on values obtained 60 minutes after the intervention session minus the value obtained 1 minute prior to the start of the treatment. (Most immune-system measures showed greater change at 60 minutes than at 5 minutes after the end of the intervention session.) Change in psychologic measures was based on the difference between the single pre- and post-treatment measures.

A *t*-test was used to compare Swedish Massage Therapy versus light touch groups with respect to their mean change in log-transformed pre- to post-treatment values as described above. There were no differences in pretreatment values for any measures between the two groups, with the exception of the CD56+ lymphocyte data; an analysis of variance (ANOVA) was performed on that one variable, co-varying for pretreatment level. The standardized treatment effect size was computed on all change scores (based on log-transformed pre- and post-test values) with a Cohen's *d*:[41]

$$\frac{(\text{Mean Change}_{\text{Massage}} - \text{Mean Change}_{\text{Touch}})}{\text{SD of Change}_{\text{Pooled}}}$$

In this preliminary stage of analysis, the current authors posit that presenting the standardized mean difference between massage and light touch provides a more useful guide for future research than statistical significance alone, as moderate-to-large effect sizes suggest areas for confirmatory study.

Results

Table 1 presents the distribution of gender, age, and self-reported race for the two treatment groups, which did not differ significantly on any of these variables. Table 2 shows the timing of the maximum or minimum post-treatment value of HPA-axis variables. Table 3 (HPA variables), Table 4 (lymphocyte data), and Table 5 (cytokine data) show the mean pretreatment, post-treatment, and change for the two groups based on raw values, along with *t*-test results and Cohen's *d* effect size based on log-transformed values.

The timing of the maximum or minimum values differed considerably across HPA-axis variables, as well as between the two treatment groups (Table 2). For the majority of subjects, the maximum post-treatment value of OT and the minimum post-treatment plasma ACTH value occurred within the first 10 minutes after the end of the treatment session. The majority of subjects had the minimum AVP value recorded later in the post-treatment period; for 48%, this occurred at the final blood draw, 60 minutes after the end of the treatment session. Minimum plasma CORT values were distributed across the range of post-treatment blood draws, from 1 to 60 minutes after the treatment session.

Consistent with the hypothesis for this research, massage was associated with a significantly larger decrease in AVP than was found for the light touch group ($p = 0.016$), with a relatively large treatment effect size of -0.74 (Table 3). Also consistent with this hypothesis, plasma and salivary CORT both showed larger decreases for massage than for light

Table 1. Demographic Characteristics of Study Participants

	Massage (n = *29*)	*Touch* (n = *24*)
Female, %	59%	50%
Age, mean ± SD, years (range)	30.7 ± 5.8 (19–45)	33.3 ± 7.3 (21–45)
Race, %		
Caucasian	55%	38%
Hispanic	7%	29%
African-American	14%	8%
Asian	17%	17%
Other	7%	8%

SD, standard deviation.

touch, although the difference on both CORT variables was not statistically significant and the treatment effect size was relatively small for these variables (−0.22 and −0.29, respectively). Findings for OT and ACTH were nonsignificant and opposite of the prediction made before the study; the touch group had a greater increase in OT (effect size −0.44) and a greater decrease in plasma ACTH (effect size +0.29) than the massage intervention group.

Although not statistically significant, the circulating lymphocyte phenotypic marker data (Table 4), demonstrate that Swedish Massage Therapy leads to a demargination of leukocytes. A single session of massage caused a moderately large treatment effect size for total lymphocytes (+0.43), CD25+ cells (+0.41), and CD56+ cells (+0.42), with smaller effect sizes for CD8+ cells (+0.31) and CD4+ cells (+0.14).

Whole-blood mitogen-stimulated cytokine production tended to be lower after a single session of Swedish massage than of light touch (Table 5). Mitogen-stimulated tumor necrosis factor-α (TNF-α) production was the only cytokine that increased more after massage than light touch (+0.25; $p = 0.456$). Production of four cytokines increased in both treatment groups, but less for massage than for touch, resulting in a negative treatment effect size for IL-1ß (−0.53), interferon-γ (IFN-γ; −0.48), IL-2 (−0.30), and IL-6 (−0.22). Production of the remaining four cytokines assessed in this study *decreased* relative to pretreatment levels for the massage group, while increasing for the light touch control group, with strong negative treatment effect sizes for IL-10 (−0.76; $p = 0.031$), IL-4 (−0.64; $p = 0.071$), IL-13 (−0.63; $p = 0.058$), and IL-5 (−0.55; $p = 0.089$).

Baseline measures on all self-report measures of psychologic symptoms were extremely low in the study sample, which excluded individuals with any *DSM-IV* Axis I psychopathology. This afforded little room for decrease in symptoms of stress or anxiety to be associated with a single session of treatment. Results for STAI State Anxiety (possible range 20–80) illustrate this, as mean baseline scores for both treatment groups were below 30. Mean scores decreased slightly more after a single session of massage compared to light touch, but the treatment effect size was negligible (−0.07; $p = 0.766$).

Discussion

The data generated in this study suggest that one session of Swedish Massage Therapy caused a relatively large decrease in AVP (as measured by effect size) and relatively small, but consistent decreases in salivary and serum CORT levels. Counter to the working hypothesis, Swedish Massage Therapy did not increase OT nor decrease ACTH, compared to the light touch control condition. Thus, these findings in healthy normal volunteers replicate reports of acute CORT decreases in a variety of pathologic conditions. The rather profound decrease in AVP observed in this study suggests at least one possible mechanism responsible for the mild, yet consistent decrease in serum and salivary CORT levels.[42,43] Although these findings represent a relatively detailed preliminary investigation of peripheral peptide measures, the findings may not reflect the central levels nor actions of these hormones.[42]

A unique feature of this study was the repeated assessment of neuroendocrine hormones at 1, 5, 10, 15, 30, and 60 minutes after the end of the intervention session. The in-

Table 2. Timing of Maximum/Minimum Post-Treatment Values for Measures of Plasma HPA Axis Variables After a Single Session of Swedish Massage Therapy Versus Light Touch

	Massage							*Touch*						
		% with maximum/minimum post-treatment value at this time							*% with maximum/minimum post-treatment value at this time*					
	N	*+1 min*	*+5 min*	*+10 min*	*+15 min*	*+30 min*	*+60 min*	N	*+1 min*	*+5 min*	*+10 min*	*+15 min*	*+30 min*	*+60 min*
OT	24							22						
Maximum post-treatment		29	29	8	12	17	4		23	18	27	5	23	5
AVP	21							23						
Minimum post-treatment		10	10	10	24	0	48		0	22	4	9	17	48
ACTH	14							11						
Minimum post-treatment		29	0	36	29	0	7		18	27	9	18	9	18
CORT	29							23						
Minimum post-treatment		14	21	10	10	10	34		26	4	13	26	9	22

HPA, hypothalamic–pituitary–adrenal; OT, oxytocin; AVP, arginine-vasopressin; ACTH, adrenal corticotropin hormone; CORT, cortisol.

Table 3. Group Means and SDs for HPA Axis Variables for Swedish Massage Therapy and Light Touch Subjects at Baseline,[a] Maximum/Minimum Post-Treatment Value,[b] and Post–Minus-Baseline Difference (Change)

	Massage		*Touch*			t-*test*		
	N	*Mean ± SD*	N	*Mean ± SD*	*Effect size*	t	df	p
OT (pg/mL)								
Baseline	24	188.39 ± 101.96	22	218.30 ± 165.11				
Maximum post-treatment		204.61 ± 103.90		245.12 ± 168.82				
Change		16.22 ± 22.77		26.82 ± 32.63	−0.44	−1.55	44	0.128
AVP (pg/mL)								
Baseline	21	63.18 ± 40.70	23	65.39 ± 53.65				
Minimum post-treatment		49.94 ± 33.48		55.99 ± 43.76				
Change		−13.25 ± 14.07		−9.40 ± 17.75	−0.74	−2.52	42	0.016
ACTH (pg/mL)								
Baseline	14	62.05 ± 14.56	11	63.70 ± 16.89				
Minimum post-treatment		50.26 ± 15.78		48.76 ± 13.87				
Change		−11.79 ± 6.42		−14.94 ± 11.26	+0.29	+0.69	23	0.494
Plasma CORT (μg/dL)								
Baseline	29	29.75 ± 16.75	23	26.75 ± 18.76				
Minimum post-treatment		18.62 ± 13.40		18.52 ± 17.43				
Change		−11.13 ± 7.57		−8.23 ± 5.42	−0.22	−0.78	50	0.441
Salivary CORT (μg/dL)[c]								
Baseline	28	0.68 ± 0.47	20	0.47 ± 0.29				
Post-treatment		0.46 ± 0.33		0.37 ± 0.29				
Change		−0.22 ± 0.38		−0.10 ± 0.20	−0.29	−0.98	46	0.330

t-tests and treatment effect sizes are calculated from log-transformed data.
[a]Average of two pretreatment values, at −5 and −1 minutes.
[b]At +1, 5, 10, 15, 30, or 60 minutes.
[c]Salivary CORT was assessed only at 1 minute before and 20 minutes after the treatment session.
SD, standard deviation; HPA, hypothalamic–pituitary–adrenal; OT, oxytocin; AVP, arginine-vasopressin; ACTH, adrenal corticotropin hormone; CORT, cortisol.

Table 4. Group Means and SDs for Lymphocyte and CD Subtypes in Swedish Massage Therapy and Light Touch Subjects (Cells/mL)

	Massage		*Touch*			t-*test*		
	N	*Mean ± SD*	N	*Mean ± SD*	*Effect size*	t	df	p
Lymphocytes								
Baseline	28	1,992,036 ± 968,840	22	2,081,364 ± 825,858				
60 min post-treatment		2,350,357 ± 882,469		2,285,909 ± 925,613				
Change		358,321 ± 518,684		204,545 ± 452,609	+0.43	+1.52	48	0.136
CD4								
Baseline	25	910,120 ± 496,189	22	927,000 ± 456,158				
60 min post-treatment		1,016,560 ± 462,648		1,024,455 ± 553,056				
Change		106,440 ± 220,421		97,455 ± 253,520	+0.14	+0.48	45	0.633
CD8								
Baseline	25	575,120 ± 277,029	22	570,500 ± 256,389				
60 min post-treatment		651,160 ± 230,765		632,591 ± 284,977				
Change		76,040 ± 130,066		62,091 ± 123,433	+0.31	+1.06	45	0.294
CD25								
Baseline	26	733,769 ± 339,579	22	707,455 ± 451,840				
60 min post-treatment		900,000 ± 412,761		761,818 ± 526,651				
Change		166,231 ± 211,604		54,364 ± 172,923	+0.41	+1.42	46	0.162
CD56								
Baseline	26	225,769 ± 118,708	22	346,305 ± 214,327		*ANCOVA*		
60 min post-Treatment		270,615 ± 116,549		385,818 ± 248,049		F	df	p
Change		44,846 ± 75,314		39,514 ± 102,421	+0.42	+0.32	1,45	0.574

t-tests and treatment effect sizes calculated from log-transformed data.
SD, standard deviation; ANCOVA, analysis of covariance.

Table 5. Group Means and SDs for Cytokine Concentrations from *in Vitro* Mitogen-Stimulated Cell Cultures from Swedish Massage Therapy and Light Touch Subjects

	Massage		*Touch*			t-*test*		
	N	*Mean ± SD*	N	*Mean ± SD*	*Effect size*	t	df	p
IFN-γ								
Baseline	19	31.87 ± 51.00	15	43.28 ± 46.56				
60 min post-treatment		44.36 ± 87.72		75.29 ± 91.47				
Change		12.48 ± 54.74		32.00 ± 49.38	−0.48	−1.41	32	0.169
IL-1ß								
Baseline	19	1.58 ± 2.13	15	1.58 ± 2.57				
60 min post-treatment		1.74 ± 1.82		2.46 ± 3.88				
Change		0.16 ± 1.39		0.88 ± 2.60	−0.53	−1.56	32	0.129
IL-2								
Baseline	17	0.39 ± 0.58	14	0.25 ± 0.20				
60 min post-treatment		0.40 ± 0.73		0.34 ± 0.42				
Change		0.01 ± 0.31		0.09 ± 0.29	−0.30	−0.82	29	0.420
IL-4								
Baseline	18	0.36 ± 0.33	14	0.76 ± 1.79				
60 min post-treatment		0.33 ± 0.32		0.92 ± 1.86				
Change		−0.03 ± 0.14		0.17 ± 0.31	−0.64	−1.87	30	0.071
IL-5								
Baseline	19	0.85 ± 1.49	13	0.87 ± 0.94				
60 min post-treatment		0.73 ± 1.19		1.30 ± 1.83				
Change		−0.12 ± 0.65		0.43 ± 1.09	−0.55	−1.76	28	0.089
IL-6								
Baseline	11	22.88 ± 16.50	10	17.37 ± 15.31				
60 min post-treatment		23.51 ± 22.32		20.31 ± 14.98				
Change		0.63 ± 19.14		2.94 ± 14.20	−0.22	−0.50	19	0.624
IL-10								
Baseline	18	34.16 ± 79.00	14	10.21 ± 14.04				
60 min post-treatment		26.07 ± 40.85		14.66 ± 21.06				
Change		−8.09 ± 50.35		4.46 ± 9.34	−0.76	−2.26	30	0.031
IL-13								
Baseline	18	8.06 ± 18.26	14	2.79 ± 4.50				
60 min post-treatment		5.40 ± 10.91		4.30 ± 6.32				
Change		−2.67 ± 7.79		1.51 ± 3.58	−0.63	−1.99	25	0.058
TNF-α								
Baseline	21	6.96 ± 9.07	16	7.03 ± 11.32				
60 min post-treatment		9.81 ± 17.72		8.23 ± 12.85				
Change		2.86 ± 15.26		1.20 ± 5.97	+0.25	−0.75	35	0.456

Data are adjusted by number of lymphocytes per mL of blood (pg/10^4cells). *t*-tests and treatment effect sizes calculated from log-transformed data.

SD, standard deviation; IFN-γ, interferon-γ; IL, interleukin; TNF-α, tumor necrosis factor–α.

formation presented in Table 2 may prove useful for determining optimum sampling times for future studies. Only the maximum or minimum value for comparison of treatment groups were selected in this preliminary study because it was believed that a broader summary of change during the hour following treatment (such as area-under-curve [AUC]) could miss evanescent, yet biologically meaningful, peaks or troughs in neuroendocrine hormones. Furthermore, one might expect a pattern of brief but potentially meaningful physiologic responses to transient environmental stimuli such as might be produced by other types of massage, or yoga or meditation.

The data presented in Table 4 demonstrate that a single session of Swedish Massage Therapy leads to a greater increase in circulating of lymphocytes than one session of the light touch intervention. There was a moderate massage versus light touch effect size for the increase in total circulating lymphocytes and cells circulating that are positive for CD25 (the α chain of the IL-2 receptor) and CD56 (a nonspecific marker of NK cells). There was a small–to–very-small effect size for the increase in the number of circulating CD4+ cells and CD8+ cells after a single session of Swedish Massage Therapy. In the majority of the published massage literature investigating the actions of massage therapy on immune function, CD56 staining is used to determine NK cell numbers. However, it has recently become accepted that CD56 can be expressed by other cells as well as NK cells; thus, although the current study's data do replicate previous reports in the literature, the current authors are hesitant to suggest that this solely reflects an increase in NK cells. In general these preliminary findings in normal volunteers—that circulating T-cells, activated lymphocytes, and CD56-positive staining cells are increased after a single session of Swedish Massage Therapy—support the findings of previous investigators who have been studying subjects with a variety of different pathologic conditions.[17–22] However,

more extensive flow cytometry studies are needed to clarify these observations. In general, the present findings are consistent with the postulate that the manual techniques used during Swedish Massage Therapy may lead to migration of leukocytes into the general circulation.

The consistently lower levels of whole-blood mitogen-stimulated cytokine production for subjects who received Swedish Massage Therapy compared to light touch was surprising. Swedish Massage Therapy caused an absolute decrease in the mitogen-stimulated production of IL-4, IL-5, IL-10, and IL-13, compared to baseline levels, while production of these four cytokines increased slightly in the light touch group. This is of particular interest, because this absolute decrease in mitogen-stimulated TH-2 cytokine levels after a single session of massage may provide a biologic basis for reports that massage therapy mitigates the symptoms of asthma in children.[9,44] Cytokine production levels of IFN-γ, IL-1ß, IL-2, and IL-6 increased relative to baseline levels in both treatment groups, but the increase was smaller for massage than for touch. Only TNF-α increased more after a session of massage than a session of light touch. In general, Swedish Massage Therapy decreased mitogen-stimulated proinflammatory, TH-1 mediated, and TH-2 mediated cytokine levels, compared to the light touch condition. Most of these differences in mitogen-stimulated cytokine levels were in the moderate-to-large effect-size range. Further work is needed to elucidate the mechanisms responsible for these findings.

As expected, the two groups of healthy normal subjects had similar baseline and postintervention ratings of anxiety, depression, and QoL. This suggests that the differences in biologic findings identified in this study were not the result of baseline or intervention-related differences in psychologic status.

There are always limitations to exploratory studies, and a number of these limitations merit discussion. Given that it was not possible to obtain from the literature a reasonable estimate of expected differences on the biologic measures investigated, this study arbitrarily settled on a sample size of approximately 25 per group. In order to decrease potential biologic heterogeneity, it was decided to study young, healthy adult subjects; thus, the current authors hesitate to extrapolate this study's findings to children or older adults. It was not possible to control for menses in this pilot analysis, although the phase of each female subject's menstrual cycle was recorded at the intervention visit, and there were no obvious differences resulting from phase of the menstrual cycle. The use of light touch condition as a control for Swedish Massage Therapy, while perhaps controversial,[45,46] allowed comparison and contrasting of the biologic effects of the core massage techniques of effleurage, petrissage, kneading, tapotement, and thumb friction while controlling for other aspects of the intervention, such as disrobing, lying on the table, physical touch, and interaction with the therapist. A different pattern of response might have been observed if another control condition had been used, but the relationship to the specific massage techniques would have been less clear. A possible criticism is that expectancy and credibility of the two interventions were not measured, but, given that the study subjects were normal individuals who were not seeking relief for a pathologic condition, it was decided that measuring these two parameters was not essential for a pilot study. The similarity in postintervention mood anxiety and QoL ratings for the two groups support this contention. Another limitation of this study is the concern that small samples may not be truly representative of the range of subject heterogeneity that can be observed in a larger sample; thus, the current effect-size estimates may be larger than would be observed in a larger replication study.[47] However, the consistency of this study's effect-size findings over a number of independent variables suggests that these biologic differences are likely to be real and replicable in a larger sample. Another possible criticism is the absence of data on sympathetic and parasympathetic tone. Heart rate variability data were collected, but these young, healthy normal subjects did not differ on any of those measures.

Conclusions

In conclusion, one session of Swedish Massage Therapy was associated with small decreases in serum and salivary CORT, but produced rather larger decreases in AVP. The data do not support the hypothesis that OT mediates changes in HPA and immune function. The data do support the notion that a single session of Swedish Massage Therapy may have fairly profound acute effects on the immune system. Many of the effect sizes noted in this investigation in normal volunteers were in the moderate range, with a few in the large effect-size range; this suggests that a larger replication study is warranted.

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Disclosure Statement

Dr. Rapaport is a consultant to Wyeth; the National Institutes of Mental Health; Dainippon-Sumitomo; Brain Cells, Inc.; Astellas Pharma; Quintiles; Pfizer; and Takeda Pharmaceuticals. Dr. Schettler is a consultant to Brain Cells, Inc. Ms. Bresee has no financial conflicts of interest.

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(Appendix follows →)

Appendix 1. Assay Details

HPA Assays

Cortisol assays had a sensitivity of 0.17 μg/dL, and intra- and interassay variabilities of 5.3% and 7.5%, respectively. ACTH assays had a sensitivity of 5.7 pg/mL with intra- and interassay variabilities of 6.8% and 10.7%, respectively. OT assays had a sensitivity of 11.7 pg/mL with both intra- and interassay variabilities of 8.7%. AVP assays had a sensitivity of 3.39 pg/mL, with intra- and interassay variabilities of 5.9% and 6.4%, respectively.

Cytokine Assays

Nine different antibodies are arrayed in triplicate spots on a nitrocellulose surface. An 8-point standard curve was used with the following ranges of detection:

- IL-1ß, IL-2, and IL-6;3–3000 pg/mL
- IL-4 and TNF-α;4–3000 pg/mL
- IL-5;10–3000 pg/mL
- IL-10 and IFN-γ;30–12,000 pg/mL
- IL-13;30–12,000 pg/mL.

After blocking for 15 minutes with 70 μL of blocking solution, each array was incubated overnight with 70 μL of 1:2 diluted whole-blood assay supernatant samples at room temperature on an orbital shaker. Samples were removed, the arrays were washed 5 times, and then incubated with 70 μL of biotinylated detection antibody cocktail containing nine detection antibodies for 1 hour. Arrays were washed again 5 times, and then incubated for 45 minutes with 70 μL of strepadvin-Cy5 solution (GE Healthcare, Piscataway, NJ). Arrays then underwent a final wash, were dried, then imaged and analyzed within 24 hours.