ORIGINAL RESEARCH

COMPOSITE EFFECTS OF GROUP DRUMMING MUSIC THERAPY ON MODULATION OF NEUROENDOCRINE-IMMUNE PARAMETERS IN NORMAL SUBJECTS

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Context • *Drum circles have been part of healing rituals in many cultures throughout the world since antiquity. Although drum circles are gaining increased interest as a complementary therapeutic strategy in the traditional medical arena, limited scientific data documenting biological benefits associated with percussion activities exist.*
Objective • *To determine the role of group-drumming music therapy as a composite activity with potential for alteration of stress-related hormones and enhancement of specific immunologic measures associated with natural killer cell activity and cell-mediated immunity.*
Design • *A single trial experimental intervention with control groups.*
Setting • *The Mind-Body Wellness Center, an outpatient medical facility in Meadville, Pa.*
Participants • *A total of 111 age- and sex-matched volunteer subjects (55 men and 56 women, with a mean age of 30.4 years) were recruited.*
Intervention • *Six preliminary supervised groups were studied using various control and experimental paradigms designed to separate drumming components for the ultimate determination of a single experimental model, including 2 control groups (resting and listening) as well as 4 group-drumming experimental models (basic, impact, shamanic, and composite). The composite drumming group using a music therapy protocol was selected based on preliminary statistical analysis, which demonstrated immune modulation in a direction opposite to that expected with the classical stress response. The final experimental design included the original composite drumming group plus 50 additional age- and sex-matched volunteer subjects who were randomly assigned to participate in group drumming or control sessions.*
Main Outcome Measures • *Pre- and postintervention measurements of plasma cortisol, plasma dehydroepiandrosterone, plasma dehydroepiandrosterone-to-cortisol ratio, natural killer cell activity, lymphokine-activated killer cell activity, plasma interleukin-2, plasma interferon-gamma, the Beck Anxiety Inventory, and the Beck Depression Inventory II.*
Results • *Group drumming resulted in increased dehydroepiandrosterone-to-cortisol ratios, increased natural killer cell activity, and increased lymphokine-activated killer cell activity without alteration in plasma interleukin 2 or interferon-gamma, or in the Beck Anxiety Inventory and the Beck Depression Inventory II.*
Conclusions • *Drumming is a complex composite intervention with the potential to modulate specific neuroendocrine and neuroimmune parameters in a direction opposite to that expected with the classic stress response. (Altern Ther Health Med. 2001;7(1):38-47)*

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> *Pythagoras of Samos, a very wise teacher of ancient Greece, knew how to work with sound. In his mystery schools in Delphi and Crotona, he taught his students how certain musical chords and melodies could produce responses within the human organism. He demonstrated that the right sequence of sounds, played musically on an instrument, can change behavior patterns and accelerate the healing process.*
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> —Ancient Greek story[1]

Drum circles have been part of healing rituals in many cultures throughout the world since antiquity. It is therefore not surprising that drumming, one of the oldest healing rituals known, is now gaining interest as a complementary therapeutic strategy in the traditional medical arena. According to

Barbara J. Crowe,[2] director of music therapy at Arizona State University, the benefits of group drumming are based on the following principles:

1. Response to rhythm is basic to human functioning, making these percussion activities and techniques highly motivating to people of all ages and backgrounds.

2. Pure percussion activities are interesting and enjoyable to all people regardless of ethnic and cultural background, musical preferences, or age range, making these activities useful in creating groups that are fun and positive for a wide variety of people.

3. Participation in active group percussion experiences has physical benefits including sustained physical activity, relaxation, and use of fine motor skills.

4. A strong sense of group identity and a feeling of belonging is created because participants are actively making music together and because the sustained repetition of the steady beat brings people together physically, emotionally, and mentally (rhythmic entrainment).

5. Percussion activities can be done with little or no previous musical background or training, making these experiences accessible to all people.

Although these principles represent ample rationale for incorporating drumming as a therapeutic intervention into conventional healthcare, a paucity of scientific data are available documenting the biological benefits associated with percussion activities. Therefore, researchers in this study set out to determine measurable biological effects associated with a group percussion activity using a controlled experimental design in normal subjects.

The initial working hypothesis was that group drumming can alter stress-related hormones and neural mediators with subsequent consequences for immunologic reactivity. A wide range of stressful environments and psychosocial factors in both human and experimental animal studies are known to alter immunological responses. When present for extended periods, such factors have been associated with adverse consequences to challenges from cancer or infectious diseases.[3-5] However, the demonstration of both diminished immunologic reactivity and increased morbidity or mortality from a tumor or infectious challenge does not necessarily mean that these observations are related causally. Such a causal link between immunologic changes and subsequent health consequences is becoming established for infectious challenge by influenza virus in mice,[6,7] wound healing in humans,[8] and breast cancer in both experimental animals[9-11] and humans.[12]

Not all stressors have an adverse impact on immune responses, particularly in acute laboratory stress paradigms. However, chronic stressors such as caregiving for a loved one with Alzheimer's disease,[13] marital separation and divorce,[14] and examination stress in medical students[14-16] appear to have a suppressive influence on many measures of immunologic reactivity.

A common pattern of dysfunction emerges in conditions of chronic or severe stress, including diminished T-cell proliferation to mitogens, diminished natural killer (NK) cell activity, diminished cell-mediated immune measures, and reactivation of latent viruses such as Epstein-Barr virus. A recent report has shown that diminished cell-mediated immunity in medical students during examination stress takes the form of shifted cytokine balance between T_H1 (interleukin [IL] 2 and interferon-gamma [IFN-γ]) and T_H2 (IL-4 and IL-10) toward a humoral and away from a cell-mediated immune response.[17]

This T_H1-T_H2 cytokine shift away from cell-mediated responses and toward humoral responses has been noted in age-associated immunosenescence[18] in patients showing a degenerating condition with cancer, even cancers normally thought of as nonimmunogenic,[19] and has been suggested to occur in individuals with human immunodeficiency virus that is rapidly deteriorating to acquired immunodeficiency syndrome.[20] Positive interventions that maintain robust cell-mediated responses, reduce perceived stress, and diminish heightened activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system may therefore be beneficial to health maintenance and wellness, even when tumors and infectious agents are involved.

These positive interventions are sometimes described as "eustress" paradigms,[21] and include exercise,[22] mirthful laughter,[21] and nature's imagery combined with music and positive affirmations.[23] However, not all hormonal responses in these paradigms are the same, either in magnitude or direction, nor is cortisol necessarily the sole mediator or even an important mediator of the stress-related immunologic alterations, especially diminished NK cell activity and diminished cell-mediated immune responses.[24]

Based on an established knowledge base of predictable neuroendocrine and neuroimmune responses described above, a protocol was established (after preliminary testing of several group-drumming approaches) to measure the ability of a single group-drumming session to modulate NK cell activity, lymphokine-activated killer (LAK) cell activity, plasma levels of IL-2 and IFN-γ, and plasma levels of cortisol, dehydroepiandrosterone (DHEA), and DHEA-to-cortisol ratios, which the researchers predicted would change in directions opposite to those expected with the classic stress response.

METHODS

Subjects and Exclusionary Criteria

A total of 111 normal age- and sex-matched volunteer subjects (55 men and 56 women, with a mean age of 30.4 years) were recruited by the Mind-Body Wellness Center in Meadville, Pa, through local newspaper advertising and word of mouth. Initially, 61 subjects were randomly assigned to 6 preliminary groups (9-11 subjects each) and studied using various control and experimental paradigms designed to separate drumming components for the ultimate determination of a single experimental model.

The final experimental design included 60 volunteers: 31 men and 29 women comprising the original composite drumming group (10 individuals) plus 50 additional subjects who participated in control or experimental group sessions. Subjects were screened extensively by phone, age and sex matched, and subsequently assigned randomly to control and experimental groups. During each telephone interview, it was explained that the subject would

be paid $25 and that venous blood sampling would occur on 2 occasions. It was further disclosed that each person would read or participate in a group-drumming exercise during a 1-hour period.

Subjects were excluded who reported active medical illnesses, or if they were receiving treatment for a medical problem or infectious disease. A history of heart or lung disease, hearing loss, pregnancy, or having missed the last menstrual period also precluded participation. In addition, volunteers were eliminated who used prescription medications other than aspirin or birth control pills. Illicit drug use, cigarette or cigar smoking, tobacco chewing, and routine consumption of more than 2 alcoholic drinks per day within the last month served as criteria for exclusion. Subjects were asked (and signed a statement agreeing) not to consume alcoholic beverages or to participate in sexual activity or aerobic exercise within a period of 24 hours prior to the experiment. All subjects refrained from eating for a minimum of 2 hours before the study. To avoid conditioning effects, subjects were also eliminated if they had drummed in the past, listened to drumming music on a regular basis, or participated in drumming within the past 3 months. Fear of blood drawing also was an exclusionary criterion.

Clinical Methods

Each group of 10 subjects arrived at the center on Mondays at 2:45 PM, 45 minutes prior to the onset of the intervention. After meeting the study coordinator in a waiting area, subjects completed and signed a written exclusionary checklist (which had been previously reviewed and checked by phone) and an informed consent. Subjects entered another room where a blood sample (approximately 30 mL) was drawn using standard Vacutainer tubes by certified and licensed laboratory technicians and nurses. A minimum of 5 staff personnel were available to facilitate immediate blood drawing within a period of less than 5 minutes for all subjects. Aliquots were immediately processed and handled according to standard laboratory procedures on site. Participants subsequently returned to the waiting area for further directions.

Each subject was provided with a clipboard and asked to fill out 2 surveys: the Beck Anxiety Inventory and the Beck Depression Inventory II. The inventories were typically completed in less than 20 minutes. Upon completion of the surveys, subjects were directed to the center's group activity area.

Control subjects sat in chairs arranged in circle formation in an open area (a room measuring 30 ft x 40 ft), and read magazines and newspapers. They were given the opportunity to read a wide selection of current magazines provided by the center. Experimental subjects participated in a group-drumming exercise according to the experimental procedure described below. Monitors were present to carefully observe all groups and to direct subjects to restrooms.

Experimental Procedures

Preliminary Protocol. Prior to designating the protocol ultimately used for the experimental intervention, 6 preliminary groups (9-11 subjects each) were evaluated using the above methodology under the following conditions: resting control—subjects read magazines, newspapers, or books during the session; listening control—subjects listened to drumming music recorded from an experimental session; basic drumming—group drumming facilitated by a community-based drumming instructor (approximately 50% instruction and 50% activity); impact drumming—group drumming facilitated by a community-based drumming instructor (approximately 20% instruction and 80% activity); shamanic drumming—group drumming facilitated using a shamanic approach; and composite drumming—group drumming facilitated by a music therapist (ultimately chosen as the treatment model based on statistical analysis).

Experimental Protocol. Each experimental group was facilitated by a music therapist or clinician with drumming experience. After brief introductions, subjects were given "shaker eggs" (plastic eggs containing sand or gravel). To establish an initial sense of teamwork and camaraderie in a lighthearted manner, the facilitator instructed the subjects to pass the shaker eggs, hand to hand, from individual to individual. The speed of transfer progressively accelerated to the point that participants could not maintain the pace, eggs were dropped, and a lighthearted response ensued.

Subjects were then instructed to choose a hand drum from a wide selection of instruments stored in an adjacent area. The facilitator provided brief percussion instructions. Each subject was then asked to tap out a simple rhythm (basically a self-designed rhythm consistent with the number of syllables in their first and last name). Thereafter, each subject played his or her respective rhythm along with other members of the group. The facilitator then varied the beat and tempo of drumming for the group for the next 20 minutes, changing tempo and volume every few minutes. With the assistance of one of the center's clinical staff, the facilitator then led the guided-imagery phase of the drumming session. Two descriptive stories were told (each approximately 15 minutes) while members of the group played their drums with a rhythm, tempo, and volume along with the facilitator in a manner that matched the spoken imagery. Subjects were allowed to keep their eyes open or closed. The entire percussion session lasted 1 hour.

Subjects were then directed to the blood drawing area, where blood samples were taken in accordance with the procedure described above. Subjects then returned to the waiting area and filled out postexperiment surveys including the Beck Anxiety Inventory and the Beck Depression Inventory II. In addition, subjects completed the Sense of Coherence Scale by Antonovsky.[25] Thereafter, subjects were paid and left the center. The protocol for these studies was approved by the Internal Review Board for Human Studies at Meadville Medical Center.

Laboratory Studies

Peripheral blood mononuclear cells (PBMCs) were isolated from 15 mL of whole blood diluted 1:1 with a wash solution of Hanks balanced salt solution supplemented with 25 mmol/L of HEPES solution and 50 µg/mL of gentamicin using density gradient media. The mononuclear cell (PBMC) layer was collected and washed twice with wash solution and once with complete media, which was RPMI-1640 supplemented with 25 mmol/L of

HEPES solution, 2 uM L-glutamine, 50 µg/mL gentamicin, and 10% fetal bovine solution. The cells were enumerated using a NOVA Celltrack 2 and adjusted to 2.5 x 10^6/mL.

Natural killer cell sensitive targets, K562 cells obtained from American Type Cell Collection (ATCC), were propagated in RPMI-1640 media, which was supplemented with 10 mmol/L HEPES, 2 uM L-glutamine, 50 µg/mL gentamicin, and 10% fetal bovine solution. On the day of the assay, the targets were labeled with 200 µCi of sterile sodium chromate 51 for 70 minutes in a 200 to 500 µL volume. The targets were washed twice prior to plating (10^4/tissue culture plate wall).

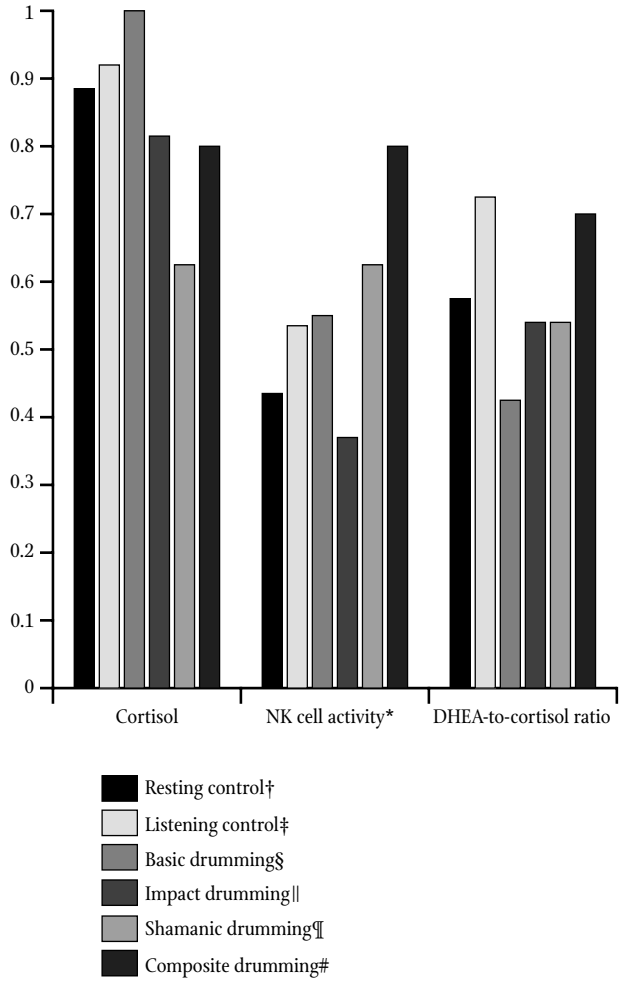
Peripheral blood mononuclear cells were used in a standard NK cell cytotoxicity assay as previously described[26] with minor modifications. Briefly, PBMCs were plated in 96 well plates with complete media, complete media containing human recombinant IL-2 (1 ng/well), or complete media containing human recombinant IFN-γ (25 ng/well). After a 45-minute incubation (37°C, 6% carbon dioxide) with media or IL-2, or a 16-hour incubation with media or IFN-γ, targets were added to obtain effector-to-target (E:T) ratios in the range of 50:1 down to 6:1. Cytokine incubations were performed at 2 E:T ratios, 25:1 and 12:1. These ratios were chosen to permit the observance of a maximal increase in cytotoxicity of all human specimens when incubated with T_H1 activators of NK cell cytotoxicity. Separate controls with media only were assessed in parallel for the 2 cytokines due to differences in incubation times. All data were generated as percent cytotoxicity.[22,27,28]

Serum levels of DHEA were measured by standard radioimmunoassay technique. Serum cortisol levels were measured by the cortisol Chiron ACS immunoassay run on the ACS:180 Automated Chemiluminescence Immunoassay Analyzer. Quantitative determination of plasma IFN-γ concentrations were performed by the IFN-γ Quantikine sandwich enzyme immunoassay. Interleukin 2 quantitation was achieved by the IL-2 Quantikine sandwich enzyme immunoassay.

Statistical Analysis

Statistical analysis of post-pre results for the 6 preliminary supervised groups (61 age- and sex-matched subjects randomly assigned to groups of 9-11 subjects each) was performed using the binomial test of proportions for the purpose of determining which protocol was most highly correlated with NK cell modulation in a direction opposite to that expected with the classical stress response. For the preliminary groups, post-pre results were calculated as a simple difference between post- and pre-measurements. The composite drumming group was the only preliminary group that demonstrated strong NK cell activity enhancement (P=.055), and therefore was subsequently selected as the treatment model (Figure 1 and Table 1).

Thereafter, pre- and postexperimental results for 60 age- and sex-matched subjects were measured by 18 assays on 30 experimental and 30 control subjects who were randomly assigned to their respective groups. Twelve assays were designated a priori as biological markers and therefore were predicted to



* NK cell activity is the sum of all dilutions.
† Subjects read magazines, newspapers, or books during the session.
‡ Subjects listened to drumming music recorded from an experimental session.
§ Subjects participated in group drumming facilitated by a community-based drumming instructor (approximately 50% instruction and 50% activity).
|| Subjects participated in group drumming facilitated by a community-based drumming instructor (approximately 20% instruction and 80% activity).
¶ Subjects participated in group drumming using a shamanic approach.
# Subjects participated in group drumming performed according to the experimental model selected for the actual study.

FIGURE 1 Preliminary drumming groups, tests of proportions. Using tests of proportions, 6 preliminary investigational groups were studied to determine the effects on cortisol and NK cell activity and the DHEA-to-cortisol ratio. The figure indicates the proportion of subjects in each group who demonstrated biological modulation in a predicted direction opposite to that associated with the classical stress response (eg, 100% of subjects in the basic-drumming group experienced reductions of cortisol). The value 0.5 indicates that 50% of the measured changes moved in the predicted direction—a finding expected by chance alone. NK indicates natural killer; DHEA, dehydroepiandrosterone.

TABLE 1 Preliminary drumming groups, tests of proportions*

	Cortisol *(P)*	NKavg† *(P)*	D:C *(P)*
Predicted direction	Down	Up	Up
Resting control (n=9)	.889	.444	.556
Binomial test	.020	‡	.500
Listening control (n=11)	.909	.545	.727
Binomial test	.006	.500	.113
Basic drumming (n=9)	1.000	.556	.444
Binomial test	.002	.500	‡
Impact drumming (n=11)	.818	.364	.545
Binomial test	.033	‡	.500
Shamanic drumming (n=11)	.636	.636	.545
Binomial test	.274	.274	.500
Composite drumming (n=10)	.800	.800	.700
Binomial test	.055	.055	.172

* The proportions indicate the frequency of preliminary group subjects with post-pre differences contrary to that expected with the classical stress response. The binomial test of proportions indicates the chance that its associated frequency could exceed .50 by chance alone. The composite drumming group demonstrated the only *P* value (.055) for NK cell activity approaching statistical significance.
† NKavg = NK cell activity - sum of all dilutions.
‡ Proportions less than .5 and hence not in the predicted direction.

NK indicates natural killer; D:C, dehydroepiandrosterone-to-cortisol ratio.

be affected by the drumming/visualization intervention (Table 2). The additional assays were used to assess sample bias, blood volume shift, blood cell demargination, affective changes, and post hoc exploratory data analysis. In view of diverse scaling of the measurements, the data were increased by 1.0 units to eliminate any negative values and allow a transformation of the data into a normalized measure of change:

$$\log([\text{postresult} + 1.0] / [\text{preresult} + 1.0])$$

The average normalized change for the experimental group was compared with that of the control group using independent *t* tests for each assay. Initially, however, an omnibus test of significance across all of the 12 assays was conducted and found to be significant (Hotelling T^2; $P < .0005$).[29] The results of multiple independent *t* tests (univariate analyses) are listed in Table 2.[30] The mean normalized change of the treatment group is compared with that of the control group in Figure 2 for the 19 tests.

RESULTS

Prior to initiating the experimental protocol, 6 groups of normal subjects were studied to determine the drumming approach to be used for the treatment group. Tests of proportions (Figure 1 and Table 1) were used to determine the proportion of subjects whose measured parameters were modulated in the predicted direction. The binomial test was performed to elucidate statistically significant trends of post-pre cortisol, NK cell activity, and DHEA-cortisol changes that occurred in a direction opposite to that expected to be associated with the classic stress response. NK cell activity was calculated as an arithmetic average of the post- minus pre- differences for all NK cell activity and LAK cell activity measures as well as E:T ratios to demonstrate a combined trend. Although all parameters reported in the actual study also were analyzed in the preliminary groups, it was determined that the "composite drumming" intervention was the only protocol that demonstrated NK cell activity enhancement in conjunction with appropriate hormonal responses (Table 1), and would thereby be used as the treatment protocol for the actual study.

The purpose of this study was to compare the biological effects of a single group-drumming intervention on normal subjects compared with controls. Hypothetical differences between treatment and control groups were tested across 12 biological markers, first globally across all 12 biological markers with a Hotelling T^2 ($P < .0005$), then individually with independent *t* tests adjusted for multiple comparisons (Table 2).

Although measures for affective change (ie, anxiety and depression), volume shifting (ie, hematocrit), and cell demargination (ie, white blood cell count) showed pre-post differences, these changes were in the same direction and magnitude for both the experimental and control groups. This finding suggests that the unique experimental milieu, rather than the treatment per se, affected these results. Therefore, random assignment of subjects to the treatment and control groups was successful in controlling for sampling bias in these areas. In addition, the Sense of Coherence Scale by Antonovsky[25] (measured once at the end of the experiment on each subject) showed no significant difference between the treatment group (mean=158) and control group (mean=150).

Serum cortisol and, to a lesser extent, DHEA—2 of the 12 designated biological markers—exhibited a similar pattern of reaction to the general milieu (within-groups effect), but not to the treatment (between-groups effect). However, for plasma DHEA there was a notable trend toward a difference between the treatment and control groups ($P = .073$). The DHEA-to-cortisol ratio showed a significant increase for within-group effects in the experimental subjects ($P = .036$).

Six of 10 NK cell assays, when expressed as mean normalized change, were significant for alpha levels adjusted for multiple comparisons (Table 2). Specifically, NK cell activity at E:T ratios of 6:1, 12:1, and IFN-γ–stimulated LAK cell activity with associated baselines for E:T ratios of 12:1 and 25:1 were significantly increased in the treatment group compared with the control group (Table 2). The other 4 assays (ie, NK cell activity at E:T ratios of 25:1 and 50:1 and IL-2–stimulated LAK cell activity at E:T ratios of 12:1 and

TABLE 2 Summary of biological markers and other assays

	Mean±SD *(P)* of pre-post comparison control group*	Mean±SD *(P)* of pre-post comparison treatment group*	Mean±SD *(P)* of treatment versus control comparison†
Biological markers			
Serum cortisol	-0.076±0.139 (.006)	-0.064±0.142 (.019)	0.012±0.036 (.747)
Plasma DHEA	-0.068±0.102 (.001)	-0.025±0.078 (.093)	0.043±0.024 (.073)
NK activity at E:T=6:1	-0.049±0.152 (.086)	0.116±0.208 (.005)	0.166±0.047 (.001)‡
NK activity at E:T=12:1	-0.034±0.147 (.213)	0.096±0.175 (.006)	0.130±0.042 (.003)‡
NK activity at E:T=25:1	-0.019±0.120 (.396)	0.048±0.193 (.179)	0.067±0.041 (.110)
NK activity at E:T=50:1	-0.027±0.113 (.205)	0.053±0.143 (.051)	0.080±0.033 (.020)
LAK with IL-2 at E:T=12:1	-0.001±0.115 (.970)	0.108±0.224 (.013)	0.109±0.046 (.021)
LAK with IL-2 at E:T=25:1	-0.018±0.088 (.270)	0.067±0.149 (.021)	0.085±0.032 (.010)
Baseline for IFN-γ at E:T=12:1	0.004±0.166 (.895)	0.314±0.427 (.000)‡	0.310±0.084 (.000)‡
LAK with IFN-γ at E:T=12:1	-0.004±0.135 (.872)	0.257±0.309 (.000)‡	0.261±0.062 (.000)‡
Baseline for IFN-γ at E:T=25:1	-0.011±0.137 (.673)	0.163±0.228 (.001)‡	0.174±0.048 (.001)‡
LAK with IFN-γ at E:T=25:1	0.005±0.117 (.807)	0.128±0.174 (.000)‡	0.123±0.038 (.002)‡
Other assays			
Beck Anxiety Inventory	-0.098±0.176 (.005)	-0.104±0.293 (.061)	-0.006±0.062 (.925)
Beck Depression Inventory II	-0.109±0.170 (.001)	-0.156±0.258 (.002)	-0.047±0.056 (.410)
Hematocrit	0.007±0.019 (.045)	0.004±0.011 (.057)	-0.003±0.004 (.388)
White blood cell count	0.042±0.053 (.000)	0.022±0.041 (.006)	-0.020±0.012 (.106)
Plasma IL-2 (a posteriori measurement)	-0.083±0.320 (.165)	-0.214±0.830 (.169)	-0.130±0.162 (.426)
Plasma IFN-γ (a posteriori measurement)	-0.062±0.205 (.108)	-0.238±0.633 (.049)	-0.176±0.122 (.153)
DHEA-to-cortisol ratio (derived)	0.004±0.052 (.670)	0.022±0.055 (.036)	0.018±0.014 (.202)

* The significance is expressed as *P* values from the paired *t* tests for the hypothesis that the normalized change was equal to zero (ie, that the experiment induced no change in the respective measurements for the control and treatment groups individually).
† The significance is expressed as *P* values from the independent *t* tests for the hypothesis that the difference in normalized change between the control and treatment groups was zero (ie, that the treatment produced no additional effect in the respective measurements for the treatment group as compared to the control group).
‡ Denotes significant *P* values for multiple comparison (alpha < .05).

DHEA indicates dehydroepiandrosterone; E:T, effector-to-target; IFN-γ, interferon gamma; IL-2, interleukin 2; LAK, lymphokine-activated killer; NK, natural killer.

25:1) showed a similar pattern of normalized change (to a lesser degree of significance) in response to treatment. In fact, each of the 10 NK cell measures with differing E:T ratios increased above the preexperimental level (ie, the mean normalized change >0) in the treatment group; 8 of 10 declined slightly (ie, mean normalized change <0) in the control group (Figure 2).

Comparison of baselines for IFN-γ–stimulated LAK cell activity at E:T ratios of 12:1 and 25:1 and for NK cell activity at E:T ratios of 12:1 and 25:1 showed an enhanced sensitivity effect for the 2 baselines due to their extended incubation times. Also, changes in natural killing ability, especially when activated by IFN-γ (eg, LAK with IFN-γ at E:T 12:1), were highly significant and clearly associated with the drumming activity. Although enhanced lymphokine activation of NK cell activity was evident in vitro, no significant in vivo changes in plasma cytokine levels were detected. Although it is possible that the time points selected in this study may not have reflected in vivo cytokine level alterations, it should also be noted that marked variability in measurements of plasma IL-2 and IFN-γ may have precluded accurate in vivo assessments.

DISCUSSION

The composite group-drumming music therapy intervention resulted in increased DHEA-to-cortisol ratios in the experimental group compared to the control group. NK cell activity was elevated by group drumming, as was (IL-2 and IFN-γ) LAK cell activity. Thus, group drumming elevated an important ratio of immunomodulatory adrenal steroids (DHEA-to-cortisol), NK cell activity, and LAK cell activity, immunologic markers of innate and cell-mediated immunity, compared with controls, in whom these neuroendocrine and immunologic measures were not altered.

Glucocorticoids, particularly cortisol in humans, are adrenal steroids that have wide-ranging anti-inflammatory effects and

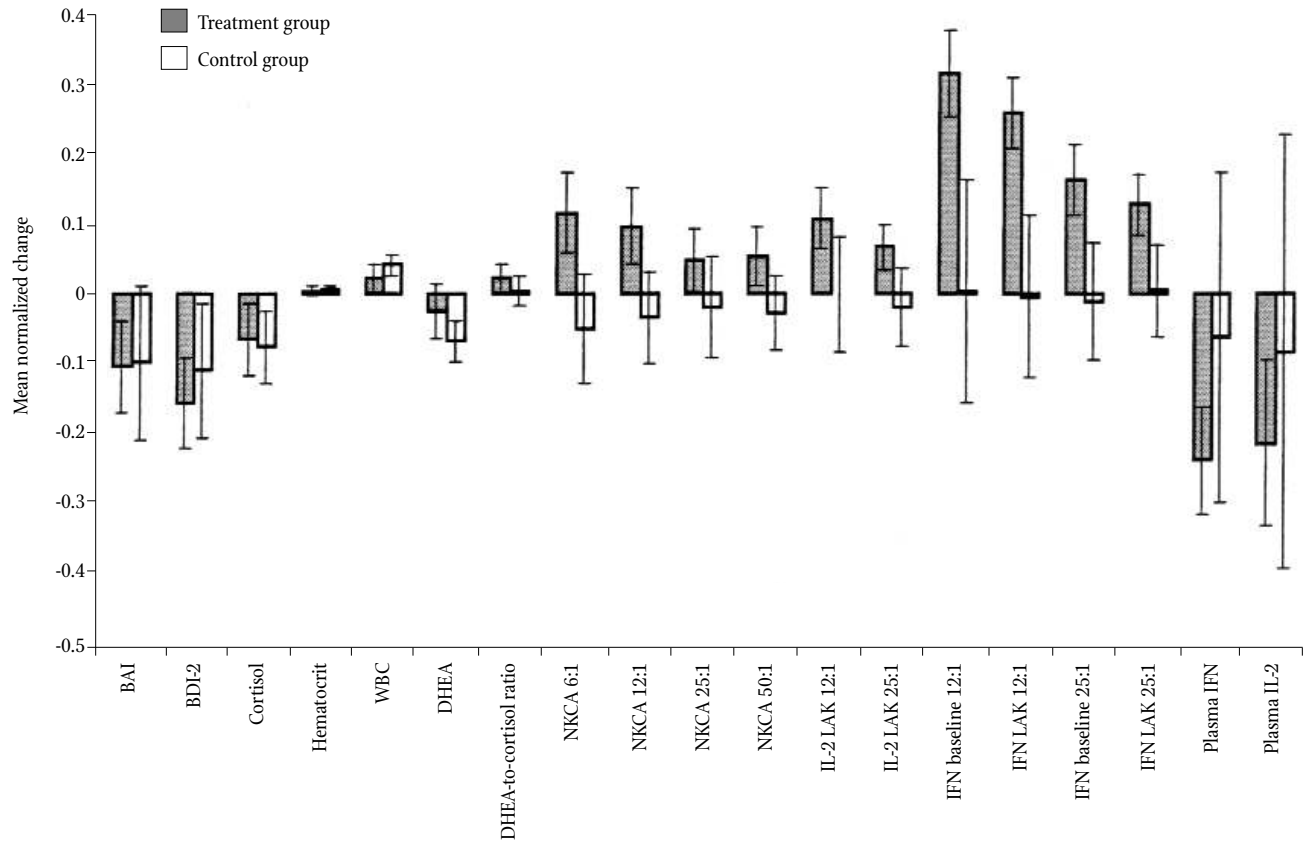


FIGURE 2 Mean normalized change (ie, log [(postresult+1.3)/(preresult+1.3)]) is plotted with 95% CI of mean indicated by error bars. Zero line indicates no difference between pretest and posttest results. Bars running in the positive direction indicate an average increase in the posttest results. A significant difference in average normalized change between the treatment and control groups would be indicated by nonoverlapping error bars for the test pair. A significant pre-postchange (within-groups effect) is indicated by error bars that do not cross zero. Natural killer cell activity 6:1 shows a significant positive change in the treatment group accompanied by a nonsignificant negative change in the control group. BAI indicates Beck Anxiety Inventory; BDI, Beck Depression Inventory; DHEA, dehydroepiandrosterone; IFN, interferon; IL-2, interleukin-2; LAK, lymphokine-activated killer; NKCA, natural killer cell activity; WBC, white blood cell.

inhibitory effects on both innate and acquired immune responses, especially in pharmacologic doses.[5,31] Not all immunologic effects of physiologic levels of glucocorticoids are inhibitory; glucocorticoids can shift the balances of helper T cell cytokine production away from T_H1 (IL-2, IFN-γ) toward T_H2 (IL-4, IL-10),[32] enhancing humoral immunity and diminishing cell-mediated immunity.

In recent years, another native adrenal steroid, DHEA, and its sulfated derivative (DHEA sulfate), as well as other related metabolites, have been shown to circulate in the blood and exert potent immunologic effects, sometimes described as antiglucocorticoid in nature.[33,34] Dehydroepiandrosterone and its metabolites can upregulate secretion of IFN-γ and IL-2 (T_H1 cytokines)[35,36] and, in experimental murine models, can protect against herpes simplex virus 1 encephalitis.[35] Furthermore, T_H1 cytokine depletion has been noted in murine acquired immunodeficiency syndrome,[36] influenza infection,[37] and West Nile virus.[38] DHEA also can augment contact sensitivity responses and exert immunostimulatory effects,[39] restore some aspects of immunosenescence,[37] and prevent some cancers.[40,41] Ben-Nathan and colleagues[38] have described DHEA as an antistress agent, based on its ability to protect mice against viral infections in the presence of a cold stressor.

Several investigators have proposed that the best way to assess adrenal steroid immunomodulatory function is through the DHEA-to-cortisol ratio.[34,42] An increase in this DHEA-to-cortisol ratio was associated with increased well-being in healthy adults in an emotional self-management program,[42] with DHEA enhancement correlating with positive affective states and diminished cortisol correlating with stress. Hechter et al[34] have proposed that diminished DHEA-to-cortisol ratios increase the risk of initiation and progression of a wide range of diseases. Van den Berghe et al[43] found that suppression of DHEA-to-cortisol

ratios in critically ill patients may aggravate or maintain the anergic state of prolonged severe illness.

The finding of elevated DHEA-to-cortisol ratios in experimental subjects in the present study suggests a shift in adrenal steroids in an immunoenhancing direction. This shift could potentially enhance cell-mediated (T_H1) immune reactivity and is consistent with enhanced LAK cell activity observed at the end of the drumming session in the experimental group. It is unlikely that the DHEA-to-cortisol ratio was elevated solely because of the exercise component of the drumming. Milani and colleagues[44] showed that exercise training alone has no significant impact on DHEA sulfate; however, behavioral therapy in combination with exercise training did elevate DHEA sulfate. In addition, qigong training in humans did not elevate DHEA sulfate or change cortisol levels.[45] Furthermore, data from preliminary studies failed to demonstrate elevations of DHEA-to-cortisol ratios associated with other drumming interventions, one of which included higher levels of exercise than ultimately used in the treatment group.

Based on the failure of some of the researchers' preliminary drumming trials to modulate neuroimmune parameters, the unique combination of components in the composite drumming sessions, including the music therapist's approach, exercise, music, and guided imagery, may have exerted a collective effect on immune modulation and adrenal steroids to elevate the DHEA-to-cortisol ratio.

Van der Berghe et al[43] have shown that DHEA and cortisol secretions are under separate central nervous system regulatory control, thereby providing ample opportunity for a complex activity such as drumming to exert emotional and cognitive influences on this central regulatory circuitry. In one preliminary study group, subjects listened to drum music generated by an experimental group. Other groups drummed without introductory warm-up activities or drumming guided imagery according to the present protocol. Another performed intense drumming without these associated activities. No significant results in any measures other than cortisol reduction were found from subjects who participated in these drumming groups. According to the present protocol, then, drumming appears to be a complex composite activity with key individual components that, in unique combination, appear to be responsible for the measured neuroendocrine and neuroimmunological changes.

NK cells are large granular lymphocytes, major components of the innate immune system, with mixed lymphocyte/monocyte/granulocyte surface markers. They are potent cytolytic cells that can kill some tumor cells, particularly bloodborne metastases and virally infected cells without the necessity of activation through an acquired immune response.[46,47] Natural killer cells are important components in maintaining health in women with breast cancer, and NK cell activity appears to be inversely related to the perception of recent past stressors in the lives of these patients.[12] Natural killer cell activity is particularly responsive to T_H1 cytokine stimulation, especially with IFN-γ and IL-2, the agents used to stimulate NK cell activity in this study. Similarly, a closely related cytolytic activity (LAK) also is stimulated by IL-2. Activities or agents that stimulate T_H1 cytokine production therefore might enhance both NK cell activity and LAK cell activity, with resultant enhancement of antitumor and antiviral defenses.

In this study, both NK cell activity and LAK cell activity were enhanced by the drumming session, but not in controls. A combination of exercise and behavioral/emotional components of the drumming session contributed to this elevation. Although it has been established that exercise itself enhances NK cell activity,[22,48,49] NK cell activity did not increase in the preliminary drumming studies using equal or higher levels of exercise.

Irwin and colleagues[50-52] have demonstrated that the brain corticotropin-releasing factor system can alter NK cell activity via sympathetic neural connections to lymphoid organs.[5] However, cortisol is not likely to play a role in modulating NK cell activity. Bodner et al[28] found no relationship in vivo between plasma cortisol and NK cell activity in healthy humans, and Irwin et al[51] were unable to find a significant relationship between serum cortisol levels and reduced NK cell activity in bereaving women. Observations in this study further reinforce the lack of correlation between cortisol and NK cell activity. In the preliminary testing of 61 subjects prior to this study, a variety of drumming activities varying in duration, intensity, and type of activity were used. During each of these preliminary sessions, the greater proportion of subjects in each group demonstrated decreased plasma cortisol levels (post-pre differences). However, with the exception of the composite drumming group (P=.055), a corresponding increase in the proportion of subjects manifesting increased NK cell activity did not approach statistical significance. In the impact drumming group, a greater proportion of subjects actually manifested diminished NK cell activity (Figure 1 and Table 1).

It is not yet known whether an increased DHEA-to-cortisol ratio could enhance NK cell activity or LAK cell activity, either directly or indirectly, via enhanced secretion of T_H1 cytokines or other immunostimulatory signals. In subsequent studies, increased attention will be paid to sympathetic noradrenergic neural activity, and the influence of other immunomodulatory neurally related hormones.[5] Only with a full temporal mapping of such immunomodulatory hormones and neurotransmitters will it be possible to better understand the mechanistic signaling basis for the enhanced NK and LAK cell activity with active drumming. At present, a wide range of possible mechanisms must be considered, including signaling effects on cell number, increased sensitivity to activation by cytokines, increased cytokine production by T_H1 cells at local sites, and changes in cell trafficking, as contributory components to the elevated NK cell activity and LAK cell activity.

Subjects participating in drumming sessions showed pre-post differences in white blood cell counts, hematocrits, and lymphocyte fractions to a similar degree and direction as control subjects. These findings support the contention that the immunologic findings in the present study are not attributable to compartment shifts (Figure 2 and Table 2). In addition, no pre-post differences existed in drumming subjects compared with controls for the Beck Depression Inventory II and the Beck Anxiety Inventory, suggesting that the experimental findings did not occur due to the presence or alleviation of preexisting anxiety or depression.

SUMMARY

This study is the first known clinical intervention using group-drumming music therapy as a modulator of biological variables in normal subjects. Both neuroendocrine and immunologic alterations were found in drumming subjects following this composite intervention compared with controls. These changes appear to be immunoenhancing (increased DHEA-to-cortisol ratios, increased NK cell activity, and increased LAK cell activity). Group-drumming music therapy, carried out according to this protocol and using a specific approach for facilitating sessions that emphasizes camaraderie, group acceptance, lighthearted participation, and nonjudgmental performance, appears to attenuate and/or reverse specific neuroendocrine and neuroimmune patterns of modulation associated with the classic stress response.

Although these data demonstrate statistically significant modulation of specific neuroendocrine and neuroimmune parameters, this study (an initial single trial design) represents only the first step in determining the ultimate value of group drumming as a wellness or therapeutic intervention. In clinical terms, it is essential to consider factors such as timing, duration, and magnitude of effects and health status. Future studies specifically addressing these issues are required before suggesting group drumming as a potential treatment strategy for individuals facing the challenges of illness.

Based on these preliminary data, however, group-drumming music therapy—in a manner similar to that of exercise, laughter, meditation, and other interventions that are practiced or enjoyed on a regular basis—has the potential to produce cumulative or sustaining neuroendocrine or immunological effects that could contribute to the well-being of an individual facing a long-term condition in which elevated NK cell activity is known to be beneficial.

Group drumming is a complex composite intervention with long-standing historical roots that encompasses the subject's full participation with physical, psychological/emotional, and cognitive involvement. Further investigation is needed to elucidate precise mechanisms of neuroendocrine and immunologic alterations, document the full duration and magnitude of these effects, and measure potential neuroendocrine and immunologic changes associated with multiple sessions over time in individuals with chronic illnesses.

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