THE UNIVERSITY OF ARIZONA.

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August 14, 2012

Mary Kilty, Executive Director
Depressive and Bipolar Disorder Alternative Treatment Foundation
450 Park Ave. 9th Floor
New York, NY 10022

Dear Ms. Kilty and Board of Directors,

Enclosed is my full proposal for support from the Depressive and Bipolar Disorder Alternative Treatment Foundation to conduct the high-impact study, "Whole body hyperthermia (WBH) for treatment of major depressive disorder (MDD)." This proposal includes:

1. Abstract
2. Scientific Section
3. Protection of Human Subjects
4. Key Personnel
5. Facilities
6. Budget
7. Key Personnel Letters

The University of Arizona accepts the application requirements and limitation on funding for this study, as indicated by the signature from Sponsored Projects on this letter. Please call me at 678-429-9870 should you have any questions. Thank you for your consideration.

Sincerely,

Charles L. Raison, MD
Associate Professor of Psychiatry
College of Medicine
Barry and Janet Lang Associate Professor of Integrative Mental Health
John and Doris Norton School of Family and Consumer Sciences

Arizona Board of Regents
for University of Arizona

Lee Anne T. Peters
Contract Officer

Sponsored Projects
University of Arizona

ABSTRACT

Despite significant advances in our scientific understanding of mental illnesses, novel therapeutic modalities with clear advantages over existing treatments have yet to be identified, leading to what the National Institute of Mental Health has referred to as a “crisis in drug development for mental illness.” Reflecting this stagnation, an international scientific seminar recently convened by the Royal Society in London concluded that “a fundamental change was needed in nearly every aspect of translational research in mental health.” Nowhere would such change be welcome than in the treatment of major depressive disorder (MDD), which is the third leading cause of overall disease burden in the world. Much of this burden comes from the fact that currently available pharmacologic modalities (which are the mainstay of treatment, especially in the USA) suffer from important shortcomings, including limited efficacy, delayed onset of action and significant side effects that impair quality of life and promote treatment non-adherence and/or discontinuation.

The current proposal is positioned to address each of these areas, by conducting a rigorous, placebo-controlled study of mild whole body hyperthermia (WBH), a novel intervention that 1) holds promise as an alternative and/or adjunct to pharmacological therapies; 2) appears to have an almost immediate and apparently long-lasting antidepressant effect; and 3) confers none of the central nervous system (CNS) mediated side-effects that bedevil other somatic therapies for depression. Our use of WBH in the current study is based on two interrelated lines of evidence. First, in a small sample of patients with severe MDD not receiving other forms of treatment we have shown that a single session of WBH produced rapid reductions in depressive symptoms that were still apparent five days following the WBH session. Although limited by a small sample size and lack of a placebo-control condition, these findings support the possibility that WBH holds remarkable promise as an antidepressant modality. Second, work by our group in animal models suggests that WBH may work via a neural pathway that runs from the skin to specific serotonin cell groups in the CNS that when activated have both antidepressant and thermoregulatory effects. Consistent with this possibility, in our depressed patients treated with WBH, reductions in depressive symptoms correlated highly with reductions in body temperature over the same time period. Moreover, patients with increased body temperatures prior to treatment had much greater responses to WBH than those with lower average body temperatures. Because inadequate functioning of the skin-to-brain pathway activated by WBH would be predicted to result in higher body temperature, these findings suggest that in addition to providing a potential therapeutic mechanism, the skin-to-brain pathway activated by WBH may contribute to disease development in at least some patients with MDD.

In conclusion, based on these preliminary findings, the current study is poised to potentially identify a safe, rapid and totally new antidepressant modality, while at the same providing a powerful impetus for evaluating the relevance of peripheral sensory pathways in general for both the pathogenesis and treatment of MDD.

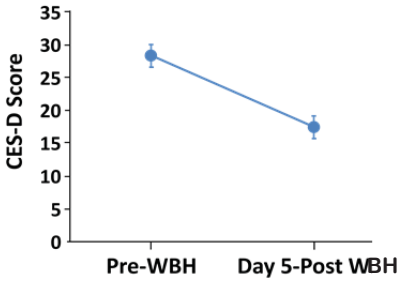
Background Information

Rationale for WBH in Depression: As the Depressive and Bipolar Disorder Alternative Treatment Foundation Board noted in response to our initial letter of inquiry, it seems counterintuitive that whole body hyperthermia (WBH) should hold promise for the acute treatment of depression given the repeated observation that major depressive disorder (MDD) is characterized by an increase in core body temperature that normalizes with successful treatment with a variety of somatic interventions.[1-5] Moreover, an inverse form of seasonal affective disorder is characterized by summer depression that seems to be brought on by the increased heat of the season.[6] Given these findings, why would one want to exacerbate the pre-existing hyperthermia of depressed people by further increasing their body temperature with WBH? Moreover, given that antidepressant medications lower brain temperature, wouldn't one want to treat depression with cold rather than heat? So again, why a proposal to use WBH to treat depression?

Three interrelated findings from our preliminary studies of WBH in depression answer these very cogent questions and provide a powerful rationale for the current proposal.

1) <u>WBH shows antidepressant effects.</u> Using an open trial design, we have now administered mild WBH to 12 medically healthy individuals with MDD, using a procedure identical to the one proposed for the current study. As **Figure 1** demonstrates, in depressed patients receiving no other therapeutic interventions, a single session of WBH produced a robust antidepressant response (assessed with the German version of the Centers for Epidemiologic Studies Depression Scale [CES-D]),[7] with mean CES-D scores dropping from 28.3 (*SD* = 9.1) pre-treatment to 17.3 (*SD* = 8.2) at 5 days post-treatment, $t(11) = 6.34$, $p < 0.001$, effect size = 1.8. Moreover, this antidepressant response was maintained 6 weeks later in 9 patients for whom these longer-term follow-up data were available (CES-D mean score 13.9). Although, this is the first study, to our knowledge, to examine WBH specifically for MDD, our findings are consistent with previous reports indicating that WBH improves mood in patients with cancer and improves quality of life scores in patients with type II diabetes mellitus.[8,9]

Figure 1.



2.) <u>WBH Reduces core body temperature and these reductions correlate with improvements in depression</u>. Given that a wide range of effective antidepressant modalities lower core body temperature (Tb core) and/or activate thermoregulatory cooling mechanisms such as sweating, one would predict that WBH should also produce chronic reductions in core body temperature. In fact, our preliminary data are entirely consistent with this prediction. We were able to obtain hourly measures of Tb core by rectal probe for 7 of our patients who received WBH. As shown in **Figure 2**, a single session of WBH significantly reduced 24-hour mean Tb core 5 days post-treatment (pre-treatment 37.3 (*SD* = 0.24); post treatment 37.0 (*SD* = 0.14), $t(6) = 5.5$, $p = 0.002$, effect size = 2.1. Moreover, reductions in Tb core from pre-treatment to post-treatment day 5 showed a large effect size, trend level correlation with reductions in depressive symptoms over the same period (**Figure 3**), $r(4) = 0.67$, $p = 0.14$, suggesting that changes in mood and Tb core may share physiological mechanisms that are accessed by WBH.

Figure 2.

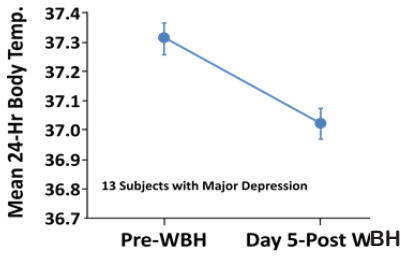
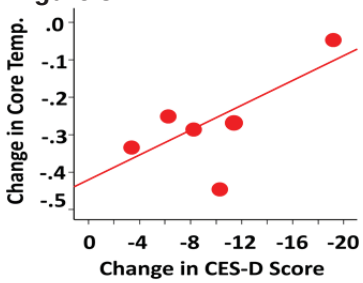
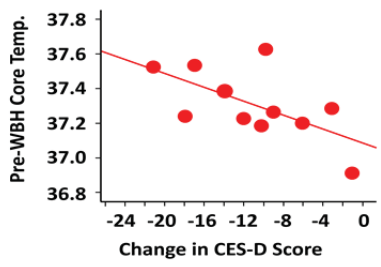


Figure 3



3.) <u>Elevated Core Body Temperature (Tb core) predicts antidepressant response to WBH</u>. If human biology was simple one would predict that depressed people with low Tb core would be most likely to benefit from heating and depressed people with high body temperature would be most likely to benefit from cooling. Interestingly, however, the opposite is clearly true, based on our preliminary data. As shown in **Figure 4**, increased 24-hour mean Tb core prior to treatment showed a large effect size, and statistically significant, correlation with improved CES-D depressive symptom responses 5 days following a single WBH session, $r(9) = 0.62$, $p = 0.043$. To our knowledge this is the first report that baseline Tb core predicts response to an antidepressant modality in general or to WBH in particular.

Figure 4.



<u>Summary:</u> These preliminary findings strongly support the potential utility of mild WBH for the acute treatment of MDD, but leave several key questions unanswered that we propose to address in the current project:

1. To what degree did non-specific placebo effects contribute to the observed behavioral outcomes and how long would the antidepressant effects of a single WBH session be maintained? We will address these issues via the

use of a rigorous, randomized placebo-controlled design described in detail below (**Specific Aim 1**), and by including a six-week follow-up period to the study design (**Specific Aim 3**).

2. What are the physiological mechanisms whereby WBH might improve depression and might these mechanisms help account for our observation of close relationships between body temperature and behavioral outcomes? We have designed **Specific Aim 2** to begin answering these questions based on a data-supported theoretical schema that helps explain why WBH may work as an antidepressant. It is to this schema and how we will begin to test it that we now turn.

Testing Bi-Directional Body-Brain Pathways Relevant to the Mechanism of Action of WBH: In this brief space we can provide only a general overview of the skin-to-brain pathway by which we suspect WBH impacts mood, based on studies by co-investigator Christopher Lowry, PhD (see **Figure 5**). More detailed discussions are available from published articles by our group, which provide references for discussion below.[10-13] Briefly, we have shown in rodent models that cutaneous warming produces an antidepressant effect and simultaneously activates serotonergic neurons in the midbrain (dorsal raphe nucleus, interfasicular part [DRI] and dorsal raphe nucleus, ventrolateral part [DRVL]) that are implicated in both thermoregulatory cooling and antidepressant and anti-anxiety behavioral effects (unpublished data and[14]). Antidepressant/anti-anxiety effects of DRI/DRVL activation are likely mediated by projections from these serotonergic nuclei to medial prefrontal cortex and limbic areas. Thermoregulatory effects of DRI/DRVL activation likely occur via projections to the anterior hypothalamus/medial preoptic area (AH/MPO) and by projections to the raphe pallidus nucleus (RPa) in the medulla, which plays an important role in the control of cutaneous sweating/vasodilation. In addition to inducing thermoregulation, heat-induced activation of the DRI/DRVL also likely impacts other behaviors and physiological processes regulated by the AH/MPO and RPa, including sleep, the circadian rhythm of cortisol and the balance between sympathetic and parasympathetic innervation to the heart, all of which are abnormal in depression, and all of which we propose to examine as potential "read-outs" of the spinoparabrachial skin-to-brain pathway activity in response to WBH in the current study. In this regard, it should be noted that hypo-activity of this skin-to-brain signaling pathway may also contribute to the pathophysiology of MDD itself, given findings (some noted above) that MDD is associated with a number of signs and symptoms predicted from sub-optimal activity in this pathway, including increased body temperature as a result of suboptimal thermoregulatory cooling ability,[1-5,15-17] decreased sweating,[15-17] diminished heart rate variability (a marker of increased sympathetic to parasympathetic signaling to the heart)[18-21] and derangements in the circadian patterning of sleep and hormonal activity, manifested as reduced sleep efficiency and flattening of the diurnal slope of cortisol.[22] *The fact that a single session of WBH resulted in longer-term thermoregulatory cooling (and thus lower core body temperature) in our preliminary study raises the intriguing possibility that the procedure may actually normalize functioning of the ascending spinoparabrachial pathway, as opposed to merely utilizing this pathway for therapeutic purposes.* The current study has been designed to begin testing these possibilities by measuring each of the "read-outs" articulated above. Moreover, recent data from Dr. Lowry's lab indicate that agents that activate DRI/DRVL serotonergic neurons reduce inflammatory and increase anti-inflammatory activity in the body, both of which are highly relevant given increasing data that peripheral inflammatory pathways contribute to the pathophysiology of depression.[23] Given the key role of inflammation in elevating core body temperature it may well be that the association between increased core body temperature and antidepressant response in our pilot study reflects the fact that WBH, like other modalities that activate DRI/DRLV serotonergic neurons, may have anti-inflammatory properties that contribute to efficacy. We will test this by measuring plasma concentrations of key inflammatory and anti-inflammatory cytokines prior to and following the study interventions. Finally, significant data demonstrate that thermosensitive cells in the skin, especially Merkel cells, are themselves serotonergic biosensors that produce brain-derived neurotrophic factor (BDNF) in response to stimulation-induced serotonin release.[10] Therefore, the effect of WBH should be indexed by increased plasma concentrations of BDNF, and these increases should correlate with clinical response, if indeed WBH operates—at least in part—via stimulation of the skin-to-brain pathway outlined above. We will assay plasma concentrations of BDNF pre- and post-intervention in the current proposal to test this possibility. *In conclusion, documenting that improvements in these physiological/biological*

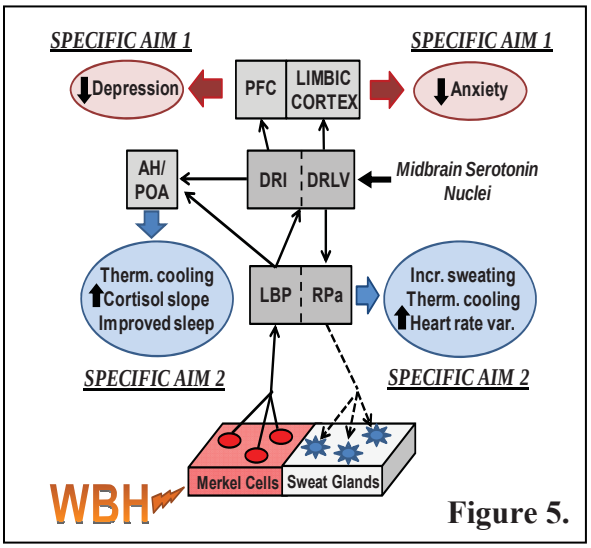


Figure 5.

factors correlate with reductions in depression would support the potentially transformative hypothesis that depression may result not just from brain abnormalities, but from abnormalities in peripheral sensory pathways. This, in turn, would encourage the development and testing of other highly novel, body-based, interventions for MDD.

Hypothesis and Specific Aims

Specific Aim 1 (Acute Effect): To evaluate the acute antidepressant effects of whole body hyperthermia (WBH) in medically healthy, antidepressant-free, adults with major depressive disorder (MDD)

Hypothesis 1: When compared to sham treatment (placebo control), a single session of WBH will induce an acute reduction in depressive symptoms that will persist for at least 5 days post treatment.

Hypothesis 1a (exploratory): When compared to sham treatment, a single session of WBH will induce an acute reduction in anxiety symptoms that will persist for at least 5 days post treatment.

Specific Aim 2 (Potential Mechanisms): To identify physiological mechanisms whereby WBH may reduce depressive and anxiety symptoms in medically healthy, antidepressant-free adults with MDD

Hypothesis 2: At 5 days post-intervention, when compared to sham treatment, a single session of WBH will a) enhance thermoregulatory cooling as demonstrated by reduced 24-hour mean core body temperature, increased skin conductance and increased number of active sweat glands; b) increase the amplitude (slope) of diurnal cortisol; c) reduce the ratio of sympathetic/parasympathetic signaling to the heart as measured by increased heart rate variability (HRV); e) improve sleep efficiency; and f) reduce plasma concentrations of BDNF and proinflammatory cytokines while increasing concentrations of anti-inflammatory cytokines.

Exploratory Research Question: To test the extent to which the effect of WBH on depressive symptom reduction is mediated independently or jointly by the physiological effects of the treatment enumerated in Hypothesis 2.

Specific Aim 3 (Effect Decay): To conduct an exploratory analysis of the decay rate of antidepressant effects following a single treatment with WBH vs. sham-WBH over a six-week follow-up period in medically healthy, antidepressant-free adults with MDD.

No Hypothesis: Preliminary data are not adequate to test a specific hypothesis for this clinically important issue, so this aim will be considered observational/exploratory, and will help inform the design of follow-up studies to the current investigations should results suggest a specific antidepressant effect for WBH at later time points.

Innovative Features

To our knowledge, the current proposal is innovative—first and foremost—because it represents the first randomized, placebo controlled trial of WBH for MDD. But we would argue that the project's innovation reaches far deeper. First, our use of WBH is informed by a novel, but empirically-supported, theoretical framework that highlights the mind-body nature of depressive pathology while at the same time accounting for why and how WBH demonstrates antidepressant properties. Accordingly, we have designed the current proposal to begin testing the effects of WBH on an integrated array of physiological/biological factors that serve as "read-outs" for the activity of the skin-to-brain spinoparabrachial pathway that we believe contributes significantly to the effect of WBH, based on basic science and clinical studies from our group, as well as the larger scientific literature. A second highly innovative feature of the current proposal is the rigor we have applied in designing the placebo condition (sham WBH) and in standardizing (and subsequently evaluating) all psychosocial interactions that occur in both active and sham WBH to ensure that active treatment doesn't exert its effects by enhancing non-specific placebo-type factors (see below for description of design of sham WBH and assessment/analysis of treatment sessions). Finally, if WBH is shown to have antidepressant properties over-and-above placebo effects, and if these effects are associated with hypothesized mechanisms of action, this will provide a powerful impetus for evaluating the relevance of other peripheral sensory signaling pathways to both the pathogenesis of MDD and its treatment.

Study Design

Study Overview: Thirty medically healthy, antidepressant-free, males and females between the ages of 18 and 60 who meet criteria for MDD and have a 17-item Hamilton Depression Rating Scale Score (HDRS) ≥ 18 at 10 days and 3 days prior to receiving the study interventions will be randomized on a 1-to-1 basis to a single treatment of either whole body hyperthermia (WBH) or sham WBH (the placebo condition). Subjects who show a ≥ 30% improvement in HDRS score between the first and second baseline assessment (i.e. between day -10 and day -3) will be considered high-likelihood placebo responders and will be discontinued from the study prior to receiving an intervention. Subjects with <30% improvement in HDRS score between baseline assessments will receive a study intervention (WBH vs. sham WBH) and will undergo assessments at post intervention day 5 and 2, 4 and 6 weeks post-intervention. Because our primary interest in the current study is to evaluate the short term effects of WBH on depressive symptom severity, the primary study endpoint will occur at 5 days post-intervention. Subsequent

assessments at weeks 2, 4 and 6 will be designed to capture the time course of decay of the antidepressant and physiological effect of either WBH or sham treatment. The selection of post-intervention day 5 as the primary study endpoint is based on preliminary data presented above. In addition to the clinician-rated and self-report measures of depression that will be included at all study visits, the assessments at "Day -3" (i.e. second baseline assessment) and the post intervention assessments at day 5 (Day +5) and week 4 will include an integrated suite of physiological measures designed to begin testing our hypothesis that WBH works via stimulation of peripheral spinoparabrachial signaling pathways that activate CNS serotonin systems to simultaneously enhance mood and induce thermoregulatory cooling. These measures will include 1) 24-hour core body temperature; 2) efficiency of thermoregulatory cooling (skin conductance level [SCL] and number of active sweat glands [ASG]); 3) sleep efficiency; 4) diurnal amplitude (slope) of cortisol; and 5) plasma concentrations of brain-derived neurotrophic factor (BDNF) and pro- and anti-inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-10 and TGF-β). These assessments will occur over 3 days at each relevant time point (see **Figure 6**, which also shows the overall study design). Details for individual design elements are discussed below.

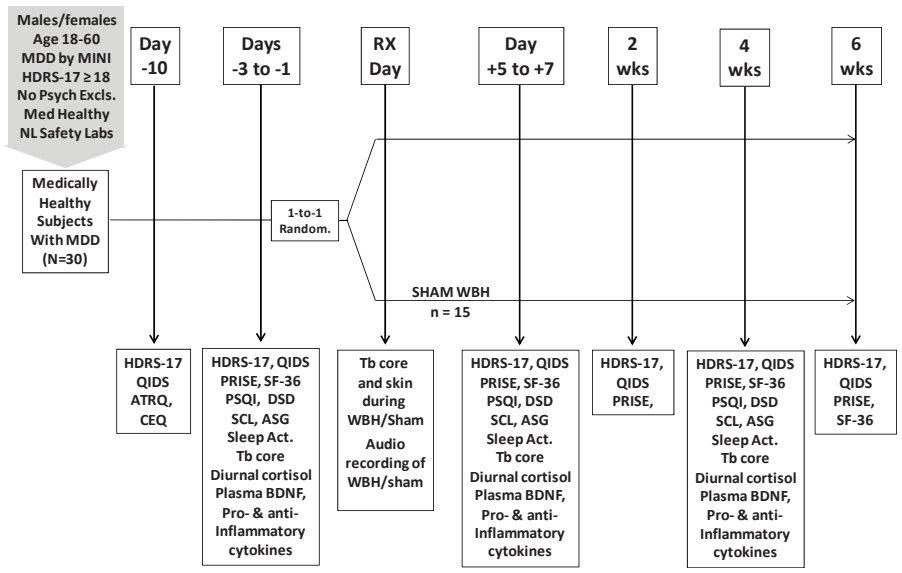


Figure 6. Legend: MDD = *major depressive disorder*; MINI = *MINI International Neuropsychiatric Interview*; HDRS-17 = *17-item Hamilton Depression Rating Scale*; No Psych Excls = *no psychiatric exclusions*; Med Healthy = *medically healthy*; NL safety labs = *normal safety labs*; QIDS = *Quick Inventory of Depressive Symptoms*; ATRQ = *Antidepressant Treatment Response Questionnaire*; CEQ = *Credibility/Expectancy Questionnaire*; PRISE = *Patient Rated Inventory of Side Effects*; PSQI = *Pittsburgh Sleep Quality Index*; SF-36 = *The Medical Outcomes Study 36-item Short Form Health Survey*; DSD = *Daily Sleep Diary*; SCL = *skin conductance level*; ASG = *number of active sweat glands*; Sleep Act. = *sleep actigraphy*; Tb core = *assessment of 24-hour core body temperature*; BDNF = *brain-derived neurotrophic factor*; RX = *treatment*

Whole Body Hyperthermia (WBH) Protocol: For both actual and sham WBH, the current study will utilize a Heckel HT3000 whole-body hyperthermia system (Heckel Medizintechnik GmbH, Esslingen, Germany, and Hydrosun Medizintechnik GmbH, Mullheim, Germany) and relevant ancillary equipment required for patient monitoring (core and skin temperature and heart rate) and software required for data acquisition and analysis. The system uses water-filtered infrared-A (wIRA) heat radiation. The Heckel HT3000 to be used for the current proposal is on loan (funded by Braun Foundation) and is already operational in the Clinical and Translational Sciences Research Center (CATS) at the Univ. of AZ.

Figure 7.

Active WBH Protocol: The active WBH protocol will use mild WBH, which has resulted in the protocol being designated as non-significant risk by the UA IRB. Chamber temperatures reach approximately 57 °C (~135 °F), and increases in core body temperature max out between approximately 38.0 – 39.0 °C. The heating phase of active WBH sessions typically lasts an hour. Subjects follow a standard body temperature response pattern to the heating. As body heat builds skin temperature rises while core temperature tends to remain unchanged, or minimally changed. As skin temperature rises, subjects begin to sweat, which stabilizes skin temperature in a plateau phase, which can last for various time periods depending on the subject. Eventually, rising core body temperature leads to an inability of sweating to maintain skin temperature and a second rise in skin temperature is observed. This second rise in skin temperature is accompanied by a spike in heart rate, indicating it is a physiological stress response. This response is used as the guide to conclude the active heating phase. The infrared lights are turned off and subjects enter a 40-minute cool-down phase in the Heckel device during which core body temperature typically continues to gradually rise while skin temperature and heart rate drop rapidly. **Figure 7** shows the Heckel HT3000 delivering actual hyperthermia.

Sham WBH Protocol (placebo condition): All procedures for sham WBH will be identical to actual WBH, with the exception that the lights that will be turned on in the device that will produce a similar color to the infrared lights but provide no heat. Heat in the box will be provided by built-in standard heating coils that will warm the air temperature enough in the box to ensure a gradual and very mild rise in the subject's skin temperature but that will not result in an increase in core body temperature. For each subject randomized to the sham WBH condition, time in the Heckel device in the faux heating phase will be matched to the time the prior subject undergoing actual WBH spent in the actual heating phase. As with actual WBH, the cool-down phase in the sham condition will be 40 minutes. This strategy will balance intervention time periods between actual and sham groups across the study.

Assessment of Depressive Symptoms, Treatment Expectations and Other Relevant Behavioral Constructs: Depressive Symptom Severity: The *17-item Hamilton Depression Rating Scale* (HDRS) will be administered by raters trained to have good intraclass correlations on the scale (i.e. >0.8) with Dr.Raison, who has extensive experience in the use of the HDRS in clinical trials. Change in HDRS score from baseline to post-intervention day 5 (day +5) will be the primary study endpoint. Secondary measures of outcome will include percentage of responders and remitters (defined as ≥50% reduction in HDRS from baseline, and an HDRS score ≤ 7, respectively) at day +5. As a secondary measure of change in depressive symptoms, the *Quick Inventory of Depressive Symptoms* (QIDS), a widely used 16-item self-report scale that is sensitive to antidepressant induced change, will be administered at each assessment. Treatment Expectations: Expectancy effects will be captured using the *Credibility/Expectancy Questionnaire* (CEQ). Past Depression Treatment History: The *Antidepressant Treatment History Questionnaire* (ATRQ) will be employed. Quality of Life: *The Medical Outcomes Study 36-item Short Form Health Survey* (SF-36) will be used to evaluate intervention-related changes in quality of life.

Assessment of Physiological Measures: Core Body Temperature will be assessed using the Equivital system with VitalSense core temperature pills (Philips Respironics), which non-invasively provide a constant measure of core temperature while passing through the GI tract prior to being expelled approximately 48 hours after swallowing. These data will be used to generate 24-hour circadian temperature curves and to calculate maximal, minimal and mean 24-hour body temperatures. Thermoregulatory cooling will be assessed by 1) skin conductance level (SCL) following the protocol outlined by Ward et al.; and 2) by counting number of active sweat glands (ASG) using a standard iodine-starch-paper technique. Heart Rate Variability (HRV) will be assessed during the period of SCL collection and will be calculated using both time and frequency domain methodologies. Sleep parameters will be measured at each assessment using standardized self-report methodologies (Daily Sleep Diary and PSQI) and via 3 nights of sleep actigraphy, which will provide objective data on sleep duration and efficiency. For the Diurnal Cortisol assessment, salivary cortisol concentrations will be obtained via a salivette methodology our group has used successfully in prior studies.[24] At the relevant assessment points, saliva will be collected over two consecutive days immediately upon awakening, between 4:30 and 6 p.m. prior to dinner and at bedtime or at 10 p.m., whichever occurs first. Cortisol amplitude, or slope, will be calculated following standardized procedures.[25] Plasma concentrations of BDNF and cytokines will be assayed by ELISA in the laboratory of Dr. Lowry.

Assessing the Role of Non-Specific "Placebo" Factors in Potential Antidepressant Effects of WBH: It is not known whether sham WBH will activate placebo-type factors as vigorously as will active WBH, which if not assessed might confound our understanding of the physiological mechanisms by which WBH exerts its effects. To address this, all WBH and sham WBH sessions will feature standardized behavior on the part of study personnel who interact with the subjects. In addition, sessions will be audio-recorded and analyzed for the degree of emotional disclosure (defined as the sharing of personal feelings, emotions, or emotionally-relevant biographical information); rated on a 1-7 Likert scale for all recorded 30 sec intervals. This analysis will be conducted by co-investigator Matthias Mehl, PhD, who is internationally recognized for his expertise with these types of analyses.

Study Population

Subjects will be males and females between age 18-60, with no exclusion for race or ethnicity. Individuals with MDD will be recruited from clinical programs within the Department of Psychiatry and by local advertisements. Subjects will meet criteria for a current major depressive episode of at least 4 weeks duration as assessed by the Mini-International Neuropsychiatric Interview (MINI) and will have a HDRS score ≥ 18 at both baseline assessments (days -10 and -3). Women with active, regular menstrual cycles will receive the study intervention during the follicular phase. Exclusionary criteria will include: 1) use of any psychotropic medications other than non-benzodiazepine hypnotics (i.e. zolpidem, zopiclone) in the four weeks prior to study entry (8 weeks for fluoxetine); 2) active substance abuse in the six months prior to study entry and/or for positive urine toxicology at screening; 3) a lifetime history of schizophrenia, bipolar I disorder or dementia; 4) presence of cardiovascular disease (treated HTN allowed), diabetes, neurological disorder, chronic infection or autoimmune conditions; 5) use of medications known to impact thermoregulatory cooling ability (e.g. beta-blockers, diuretics, antihistamines); 6) a positive pregnancy test or an intention to become pregnant during the study; and 7) metallic or silicone implants. Potential

subjects may also be excluded at the discretion of study personnel if judged to be unlikely to successfully engage with the study protocol as a result of comorbid psychiatric or medical issues or as a result of logistical problems with participation.

Statistical Analysis

T tests and chi-square analyses (or Fisher's Exact Test where appropriate) will be used to compare baseline sociodemographic, biological and clinical variables between subjects randomized to WBH or sham WBH. Should baseline differences be identified (i.e. randomization failure) these factors will be treated as covariates for all subsequent analyses. All data will be evaluated for normality, and appropriate procedures will be performed in cases where normality is violated (e.g. log transformation of data, use of appropriate non-parametric tests). Strategies for testing study hypotheses, exploratory questions and aims are as follows:

Hypothesis 1 and 1a: *When compared to sham treatment (placebo control), a single session of WBH will induce an acute reduction in depressive symptoms that will persist for at least 5 days post treatment*

Analytic Strategy: An intent-to-treat analysis using a *mixed-effects model for repeated measures* (MMRM) will be employed to analyze the change from baseline of HAM-D-17 and Spielberger Trait anxiety scores as a function of treatment group, time and their interaction (included assessments: day -10, day -3 and post-intervention day 5 [day +5]). These analyses will be complemented by comparing rates of response/remission at day +5 using Chi-Square.

Hypothesis 2: *When compared to sham treatment, a single session of WBH will reduce 24-hour mean core body temperature, improve sleep efficiency and increase the amplitude (slope) of diurnal cortisol at five-day follow-up.*

Analytic Strategy: An intent-to-treat analysis using MMRM will be employed to analyze the change from baseline in 24-hour mean core body temperature, sleep efficiency as a function of treatment group, time and their interaction (included assessments: day -3 [baseline] and post-intervention day 5 [day +5]).

Exploratory Research Question*: Test the extent to which the effect of WBH on depressive symptom reduction is mediated independently or jointly by the physiological and the behavioral (i.e. disclosure) effects of the treatment*

Analytic Strategy: A multiple mediation model (with physiological and behavioral variables) will be evaluated following the procedure established by Preacher and Hayes.[26] Randomized group (WBH vs. sham treatment) will be the independent variable and reduction from baseline to 5 days post treatment will be the dependent variable. Preacher and Hayes' multiple mediation model allows for the simultaneous testing of multiple indirect paths. Because of the lack of prior research on mechanisms underlying WBH and consistent with the exploratory nature of the research question, we will first test each potential physiological/biological mediator individually using the resampling (bootstrapping) procedure that Preacher and Hayes developed specifically for small sample sizes.[27] Once evidence of simple mediation (or lack thereof) is established for each of the four variables, a stepwise model of multiple mediation will be built. The final model will yield exploratory evidence about how the potential mediator variables act independently or jointly to reduce depressive symptoms through WBH (vs. sham treatment).

Specific Aim 3 (Effect Decay): *To conduct an exploratory analysis of the decay rate of antidepressant effects following a single treatment with WBH vs. sham-WBH over a six-week follow-up period in medically healthy, antidepressant-free adults with MDD*

Analytic Strategy: An intent-to-treat analysis using MMRM will be employed to analyze the change from baseline of HAM-D-17 scores as a function of treatment group, time and their interaction (included assessments: baseline assessments at day -10, day -3 and post-intervention assessments at day 5, 2 weeks, 4 weeks and 6 weeks). A regions-of-significance test will be conducted following procedures established by Preacher, Curran, and Bauer to the value of time (i.e. from what time point on) at which the slope for the WBH group fails to be significantly different from the slope for the sham treatment group.[28]

Potential Public Health Impact

Despite significant advances in our scientific understanding of mental illnesses, novel therapeutic modalities with clear advantages over existing treatments have yet to be identified, leading to what Thomas Insel, Director of the National Institute of Mental Health has referred to as a "crisis in drug development for mental illness".[29] Reflecting this stagnation, an international scientific seminar recently convened by the Royal Society in London concluded that "a fundamental change was needed in nearly every aspect of translational research in mental health".[29] Nowhere would such change be welcome than in the treatment of depression, which is the third leading cause of overall global disease burden.[30] Much of this burden comes from the fact that currently available pharmacologic modalities (which are the mainstay of treatment, especially in the USA) suffer from important shortcomings, including limited efficacy, delayed onset of action and significant side effects that impair quality of life and promote treatment non-adherence and/or discontinuation. The current proposal is positioned to address each of these areas, by offering a novel intervention that 1) holds promise as an alternative and/or adjunct to pharmacological therapies; 2) has an almost immediate and apparently long-lasting antidepressant effect; and 3) confers none of the CNS mediated side-effects that bedevil other somatic therapies for depression.

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PROTECTION OF HUMAN SUBJECTS

The University of Arizona IRB has deemed the Heckel HT3000 WBH system a non-significant risk (NSR) device for investigational use in this study. Subjects randomized to WBH will be induced to levels of heat comparable to a mild fever (100-101.3°F) over an average period of 2 hours 20 minutes. Earlier research conducted by a colleague at University of Texas Houston Health Sciences Center under their own NSR determination found patients tolerate WBH protocols physiologically and without verbal complaint until core body temperature reaches 40.0 °C for periods up to 6 hours. The present study only increases core body temperature to approximately 38.5-39.0°C. The WBH system includes patient monitoring (temperature, EKG, oxygen consumption, blood pressure and respiration) and recording software. The ambient temperatures used are well below those normally achieved in a sauna. Skin temperatures typically reach 38-42 °C; increases in skin temperature during challenge are typically 8-10 °C.

Research staff have completed IRB-approved human subjects training programs. Potential study participants will be screened by study staff to evaluate whether they meet trial inclusion and exclusion criteria. Rigorous screening procedures will be used to screen out persons with health problems who might be at higher risk of adverse events. The following data will be obtained for screening and/or research purposes: whole blood and urine, EKG recordings, skin and core body temperature recordings, medical and psychological history, health history, diagnosis of MDD. We will collect information about psychiatric history, including previous treatment and medical history, including requests for records from previous providers. Data collected in the trial will be obtained from clinician interviews, structured self-report rating scales, and audiorecordings of the WBH sessions. We will collect blood samples for measurement of plasma BDNF and pro- and anti-inflammatory cytokines. A pregnancy test will be conducted at screening, immediately prior to starting the WBH procedure, and at the end of study participation, to ensure female subjects are not pregnant. Medical staff will use standard sanitary biological specimen collection safety protocols for collection and processing of samples. Mobile devices will be used to capture physiological information on 24h diurnal rhythms, including core body temperature (Philips Respironics Equivital system with VitalSense core temperature pills), and sleep physiology (nightly recordings at home using actiwatches, no known risk). Saliva will be collected for analysis of cortisol diurnal rhythm. Patients with gastrointestinal disorders or a history of difficulty swallowing food or large capsules will be excluded to reduce adverse events due to use of Equivital capsule temperature pills. If subjects leave the laboratory prior to passing the temperature pill, we will ask them to wear a bracelet that indicates that they have a temperature pill inside their body and that MRI should not be performed. The pill will exit the body in a bowel movement approximately 1-5 days after ingestion.

Subjects will be shown the WBH system prior to the study and procedures will be described in detail to ensure that there is no misunderstanding of the protocol. Subjects will be informed that the temperature inside the device will vary depending on the level of heat they are randomized to receive, and they can stop the protocol at any time. A trained research staff and physician will be present to monitor all aspects of the procedure (including patient physical responses) for all active and sham sessions. Questionnaires that include suicidal items will be immediately reviewed by Drs. Raison or Thienhaus, both board certified psychiatrists. Suicidal ideation will be dealt with appropriately, based on physician assessment. All depressed patients will be closely monitored throughout their period of participation in the study for signs of significant clinical worsening, with particularly close monitoring for the development of suicidal ideation. Patients who demonstrate substantial worsening in depressive severity during the trial will be discontinued and will be referred for appropriate follow-up treatment. Subjects will be instructed to tell the investigator if they have anxiety, claustrophobia, or history or family history of blood clotting problems/disorders. To reduce risk of blood clotting, subjects will be asked to stretch and tense leg muscles periodically. Based on our conversations with other clinicians in the U.S. and Europe, any mild drowsiness following the session should resolve within 30 minutes. Subjects will remain in the facility for about 1 hour following the session for observation and questionnaires. If after that time they indicate continued drowsiness, subjects will be required either to have an adult with a valid driver's license drive them home or be willing to have a cab take them home (paid for by the study).

All study information gathered and records generated will be kept locked with appropriate protection to maintain confidentiality. Research records will only be released with the subject's written permission. Data will be coded with an indirect identifier. All assessments will occur at the Clinical and Translational Science (CaTS) research facility or the Department of Psychiatry at the University of Arizona, and hence a private location bound by rules of patient confidentiality. The identity of subjects will be known only to the PI and approved research staff. The raw data will be kept under lock for 6 years from the completion of the study and then destroyed. We have applied for a "Certificate of Confidentiality" to provide maximal protection against any agency forcing investigators to release subject information. The proposed clinical trial will be registered at Clinicaltrials.gov. To ensure timely safety monitoring, an internal review of data will be conducted monthly in collaboration with Drs. Raison/Thienhaus. A Data Safety Monitoring Board will provide regular oversight of study activities.

KEY PERSONNEL

Biosketches are included for the following key personnel on this proposal:

Charles Raison, MD, (Principal Investigator) is an Associate Professor of Psychiatry and the Barry and Janet Lang Associate Professor of Integrative Mental Health at the Norton School of Family and Consumer Sciences (NSFCS) at the University of Arizona. Dr. Raison will oversee all aspects of the study, including consulting with co-investigators, subject recruitment/screening/psychiatric evaluation, acquisition and analysis of behavioral/psychosocial and biological data, day-to-day administration of the project, oversight of data security, writing of progress reports and communication with sponsor, and data analysis and reporting of findings. Dr. Raison has 10% protected time (1.2 calendar months) reserved for innovative research on this project.

Christopher A. Lowry, PhD, (Co-investigator) is an Assistant Professor in the Department of Integrative Physiology and Center for Neuroscience at the University of Colorado, Boulder. As co-investigator, Dr. Lowry will conduct baseline and follow-up measurements of plasma concentrations of brain-derived neurotrophic factor (BDNF), interleukin 6 (IL-6), IL-1β, tumor necrosis factor alpha (TNFα) and IL-10. We are requesting support for 2% effort or 0.24 calendar months.

Matthias Mehl, PhD, (Co-investigator) is an Associate Professor of Psychology at the University of Arizona. Dr. Mehl will be responsible for input on the standardization of study staff-participant interactions during WBH and sham sessions, and input on the design for transcribing audiotaped treatment sessions.

Ole J. Thienhaus, MD, (Co-investigator) is a Professor and Chair of the Department of Psychiatry at University of Arizona. Dr. Thienhaus will work with Dr. Raison regarding participant safety during WBH and sham procedures, and in terms of risks inherent in subject population, e.g., depression, suicide.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Raison, Charles L.	
eRA COMMONS USER NAME	Associate Professor
craison	

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Stanford University, Stanford, CA	B.A.	1976-80	Anthropology
University of Denver, Denver, CO	M.A.	1982-1984	English
Washington University School of Medicine	M.D.	1987-91	Medicine
W. Los Angeles VA Med Ctr and UCLA-NPI	Intern	1991-92	Rotating
UCLA Neuropsychiatric Institute, L.A., CA	Residency	1992-95	Psychiatry

A. Personal Statement

I have extensive experience relevant to my role as principal investigator (PI) for the current project. Of most direct relevance, I served as PI on an NIH-funded randomized, placebo-controlled trial of the cytokine antagonist infliximab for treatment resistant major depression (MDD). This study involved the recruitment and study over 12 weeks of a group of severely depressed outpatients. The study was successfully concluded and results are scheduled for publication in *Archives of General Psychiatry* in September 2012. As in the current study, our work with infliximab focused on testing the concept that modulation of peripheral body-to-brain signaling pathways (peripheral inflammation in this case) might hold promise for the development of novel antidepressant strategies. Many of the assays and methodologies that I successfully employed in this and other prior studies will be incorporated in the current protocol, which significantly increases the likelihood that the current project will be brought to successful completion. In addition to expertise in the design, implementation and interpretation of data from rigorous clinical trials of novel antidepressant strategies I have extensive experience as PI for large-scale projects at both the basic science and clinical-translational level. Based on this expertise, I have a long track record of successful NIH grant support that has resulted in a number of high impact publications.

B. Positions and Honors (selected):

1998-1999	Chief Resident, Adult Inpatient Services, UCLA Neuropsychiatric Institute and Hospital, Los Angeles, CA
1995-1999	Assistant Clinical Professor, UCLA Neuropsychiatric Institute, Los Angeles, CA
1995-1999	Director, Emergency Psychiatric Services, UCLA Neuropsychiatric Institute and Hospital, Los Angeles, CA
1998-1999	Associate Director, Consultation & Evaluation Services, UCLA Neuropsychiatric Institute and Hospital, Los Angeles, CA
1999-2001	Assistant Professor (Clinical Track), Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA
2002-	Assistant Professor (Tenure Track), Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA
1999-2002	Director, Consultation & Liaison Psychiatric Services, Grady Health System, Atlanta, GA
2004-2011	Director, Behavioral Immunology Clinic, Mind-Body Program, Emory University School of Medicine, Atlanta, GA
2007-2011	Clinical Director, Emory Mind-Body Program
2010-2011	Associate Professor, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA

2011-	Associate Professor, Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ
2011-	Barry and Janet Lang Associate Professor of Integrative Mental Health, John and Doris Norton School of Family and Consumer Sciences, University of Arizona, Tucson, AZ
2005-	Ad hoc Reviewer for Department of Veteran Affairs Career Development Awards
2005-	Ad hoc Reviewer for National Institute of Mental Health BSTART program
2006	Member, Special Emphasis RFA panel for "Neuroimmune Mechanisms and Chronic Fatigue Syndrome" RFA-OD-06-006, National Institutes of Health
2006	Member, Special Emphasis panel (ZMH1-ERB-S-07) for "HIV and Psychiatric Comorbidity Research Project" RFA-MH-07-020 and -21, National Institutes of Health
2006	Ad hoc Reviewer for Health Review Board of Ireland
2006-	Co-Director, Emory Collaborative for Contemplative Studies
2007	Co-Chair, External Blue Ribbon Panel (EBRP) called to review the Chronic Fatigue Syndrome Research Program within the Centers for Disease Control and Prevention, Atlanta, GA
2007-	Member, Small Grants for Behavioral Research in Cancer Control Council ZCA-1 SRLB-H 01 S. National Cancer Institute
2008-	Mental Health Expert, CNN.com
2010	Member, Special Emphasis Panel/Scientific Review Group 2010/05 ZAT1 PK (currently active)
2013	Have agreed to join the NIH MESH Study Section
1991	Alpha Omega Alpha, Washington University School of Medicine Chapter
1991	Missouri State Medical Association Award
1993-1994	Fellow of the American Psychoanalytic Association
2001	Emory University Psychiatry Residents' Outstanding Educator Award
2001	Emory University Teaching Fund Award
2003	Emory University Medical Students' Teaching Award for Psychiatry
2005	Emory College Seed Fund Award to Improve the Research Profile of the Arts and Sciences
2006	Emory Strategic Initiatives Award to fund Collaborative for Contemplative Studies
2006	Emory College Seed Fund Award to Improve the Research Profile of the Arts and Sciences
2006	Emory University Teaching Fund Award
2011	Distinguished Visiting Professorship, Brooke Army Medical Center
2011	Champion of Hope Award, Africa's Children's Fund

C. Selected peer-reviewed publications

Raison, C.L. & Miller, A.H. When Not Enough Is Too Much: The role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *American Journal of Psychiatry*. 2003;160: 1554-1565. PMID: 12944327.

Capuron, L., Raison, C.L., Lawson, D.H., Musselman, D.L., Su, C., Nemeroff, C.B., Miller, A.H. An exaggerated HPA axis response to initial injection of interferon-alpha is associated with depression during interferon-alpha therapy. *American Journal of Psychiatry*, 2003; 160(7): 1342-1345. PMID: 12832253.

Raison, C.L., Demetrashvili, M., Capuron, L., Miller, A.H. Depressive symptoms and viral clearance in patients receiving interferon-alpha and ribavirin for hepatitis C. *Brain, Behavior and Immunity*, 2005: 19: 23-27. PMID: 15581735.

Raison, C.L., , Borisov, Broadwell, S.D., A.S., Manatunga, A.K., Woolwine, B.J., Jacobson, I.M., Nemeroff, C.B., Miller, A.H. Depression during pegylated IFN-alpha plus ribavirin therapy: prevalence and prediction. *Journal of Clinical Psychiatry*, 2005; 66: 41-48. PMID: 15669887.

Raison, C.L., Capuron, L., Miller, A.H. Cytokines sing the blues: inflammation in the pathogenesis of depression. *Trends in Immunology*, 2006; 27: 24-31. PMID: 16316783.

Raison, C.L., Woolwine, B.J., Binongo, J., Demitrashvili, M.F., Borisov, A.F., Weinreib, R., Staab, J.P., Zajecka, J.M., Bruno, C.J., Henderson, M.A., Reinus, J.F., Evans, D.L., Asnis, G.M., Miller, A.H. Paroxetine for Prevention of Depressive Symptoms Induced by Interferon-alpha plus Ribavirin for Hepatitis C. *Alimentary Pharmacology & Therapeutics* 2007; 25(10): 1163-74. PMID: 17451562.

Raison, C.L., Woolwine, B.J., Borisov, A.S., Cowles, M.K., Alagbe, O., Vogt, G., Miller, A.H. Effects of interferon-alpha on diurnal hypothalamic-pituitary-adrenal axis activity and behavior in patients with hepatitis C. *Molecular Psychiatry* 2008, Epub. PMID: 18521089.

Pace, T.W.W., Negi, L.T., Adame, D., Cole, S.P., Sivilli, T.S., Brown, T., Issa, M.J., Raison, C.L. Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. *Psychoneuroendocrinology* 2009; 34(1): 87-98. PMID: 18835662.

Raison, C.L., Borisov, A.S., Woolwine, B.J., Vogt, G.J., Massung, B. Miller, A.H. Activation of CNS inflammatory pathways by interferon-alpha: relationship to monoamines and depression. *Biological Psychiatry* 2009; 65(4): 296-303. PMID: 18801471.

Raison, C.L. Lin, J.S., Reeves, W.C. Association of high-sensitivity c-reactive protein with chronic fatigue in a population-based sample, *Brain, Behavior and Immunity* 2009; 23(3): 327-27. PMID: 19111923.

Miller, A.H., Maletic, V., Raison, C.L. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression, *Biological Psychiatry* 2009; 65: 732-41: PMID: 19150053.

Pace, T.W.W., Negi, L.T., Sivilli, T.I., Issa, M.J., Cole, S.P., Adame, D.D., Raison, C.L. Innate immune, neuroendocrine and behavioral responses to psychosocial stress do not predict subsequent compassion meditation practice time. *Psychoneuroendocrinology* 2010; 35: 310-5: PMID: 19615827

Raison, C.L., Dantzer, R. Kelley, K.W., Lawson, M.A., Woolwine, B.J., Vogt, G., Spivey, J.R., Saito, K., Miller, A.H. CSF Concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: Relationship to CNS immune responses and depression. *Molecular Psychiatry* 2010;15: 393-403: PMID: 19918244

Raison, C.L., Rye, D.B., Woolwine, B.J., Vogt, G., Bautista, B.M., Spivey, J., Miller, A.H. Chronic Interferon-Alpha Administration Disrupts Sleep Continuity and Depth in Patients with Hepatitis C: Association with Fatigue, Motor Slowing and Increased Evening Cortisol. *Biological Psychiatry* 2010; 68: 942-9: PMID: 20537611

Raison, C.L., Lowry, C.A., Rook, G.A.W. Inflammation, Sanitation and Consternation: Loss of Contact with Co-Evolved, Tolerogenic Micro-Organisms and the Pathophysiology and Treatment of Major Depression, *Archives of General Psychiatry* 2010; 67: 1211-24: PMID: 21135322

Felger, J.C., Alagbe, T., Pace, T.W.W., Woolwine, B.J., Raison, C.L., and Miller AH. Early activation of p38 mitogen activated protein kinase is associated with interferon-alpha-induced depression. *Brain, Behavior and Immunity* 2011; 25(6): 1094-8: PMID: 21356304

Haroon, E., Raison, C.L., Miller, A.H. Psychoneuroimmunology Meets Neuropsychopharmacology: Translational Implications of the Impact of Inflammation on Behavior. *Neuropsychopharmacology* 2012; 37: 137-62: PMID: 21918508

Felger, J.C., Cole, S.W., Pace, T.W.W., Hu, F., Woolwine, B.J., Doho, G.H., Raison, C.L., Miller, A.H. Molecular Signatures of Peripheral Blood Mononuclear Cells during Chronic Interferon-alpha Treatment: Relationship with Depression and Fatigue. *Psychological Medicine* 2011; 42: 1591-603: PMID: 22152193

Raison, C.L. & Miller, A.H. Is depression an inflammatory disorder? Current Psychiatry Reports 2011;13:467-75: PMID: 21927805

Rook, G.A., Raison, C.L., Lowry, C.A. Can we vaccinate against depression? *Drug Discovery Today* 2012; 17: 451-8; PMID: 22507593

Raison, C.L. & Miller, A.H. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). *Molecular Psychiatry* 2012; Epub: PMID: 22290120

Pace, T.W., Negi, L.T., Dodson-Lavelle, B., Ozawa de-Silva, B., Reddy, S.D., Cole, S.P., Danese, A., Craighead, L.W., Raison, C.L. Engagement with Cognitively-Based Compassion Training is associated with reduced salivary C-reactive protein from before to after training in foster care program adolescents. *Psychoneuroendocrinology* 2012; Epub; PMID:22762896

Raison, C.L., Haroon, E., Woolwine, B.J., Shuo, C., Haber, M., Rutherford, R., Miller, A.H. Safety and efficacy of the tumor Necrosis factor-alpha antagonist, infliximab, for treatment resistant depression: A double-blind, randomized clinical trial. *Archives of General Psychiatry* 2012; in press.

Mascaro, J.S., Rilling, J.K., Negi, L.T., Raison, C.L. Compassion meditation enhances empathic accuracy and related neural activity. *Social Cognitive and Affective Neuroscience* 2012; in press

C. Research Support

Ongoing Research Support

R01AT004698 Raison (PI)
Mechanisms of Meditation. 05/01/09—03/31/14
This study seeks to examine issues of specificity, dose response and physiological effects of compassion meditation, with the long term goal of better identifying specific meditative practices that might be especially relevant to the prevention of diseases related to stress-induced activation of inflammatory pathways.

R01AT007297 Raison (PI)
Inflammation, Stress, and Social Behavior: 10/01/11-09/30/15
Using Ecological Assessments and Model Systems
This study seeks to examine the effect of chronic inflammatory activation, using treatment with interferon (IFN)-alpha as a model system, on real world social behavior, as well as the role of changes in stress responsivity, in mediating cytokine-induced behavioral changes.

3R01AT004698-01A1S1 Raison (PI)
Mechanisms of Meditation—SUPPLEMENT 09/01/12—08/31/14
This study adds to the parent Mechanisms of Meditation project by adding the investigation of real world, daily-life speech and behavior to the study. The goal of this supplement is to examine whether different meditation techniques have specific effects on prosocial speech and behavior and whether changes in stress responsivity and sleep mediate these effects.

Past Research Support (selected)

R01 MH070553 Raison (PI) 12/01/04-11/30/09
Cytokine-CRH Interactions in IFN-alfa-induced Depression
This project determines risk factors for the development of major depression in patients receiving interferon-alpha (IFN-alpha) treatment, focusing on bi-directional neuroendocrine—innate immune system pathways relevant to the development of depression in the context of medical illness.

K23 MH64619 Raison (PI) 1/01/02 – 12/31/06
Glucocorticoid Resistance in Immune-Based Depression
A five-year K23 career development grant that examined the effect of the proinflammatory cytokine interferon-alpha-2-beta (IFN-alpha) on the development of resistance to the effects of glucocorticoids and the relationship between this resistance and the development of depression during treatment with IFN-alpha.

R21 MH0771172-01 Raison (PI) 01/01/08-12/31/09
Neurobiological and Behavioral Effects of Cytokine Antagonism in Major Depression.
This study seeks to evaluate the role of proinflammatory cytokine activity in the pathogenesis and treatment of major depression via the novel strategy of administering an antagonist to the cytokine Tumor Necrosis Factor-alpha in medically healthy patients with treatment resistant major depression.

Georgia Department of Human Services Raison (PI) 05/24/10-10/15/10
A Study of Cognitively-Based Compassion Training (CBCT) to Enhance Health and Well-Being in Adolescents in Foster Care in Metropolitan Atlanta
This study is examining whether 6 weeks of Cognitively-Based Compassion Training (CBCT) will improve an array of behavioral endpoints as well as salivary cortisol, amylase and C - reactive protein in adolescents in foster care, compared to a wait-list control condition.

R01AT004698-01S1 Raison (PI)
Mechanisms of Meditation—ARRA SUPPLEMENT 10/01/09—09/31/11
This study adds to the parent Mechanisms of Meditation project by adding the investigation of real world, daily-life speech and behavior to the study. The goal of the Competitive Revision is to examine whether different meditation techniques have specific effects on prosocial speech and behavior.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
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NAME	POSITION TITLE
Christopher Alan Lowry	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) chrislowry	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Wyoming, Laramie, Wyoming	B.A. Honors	1983-1987	Zoology
Oregon State University	Ph.D.	1987-1995	Zoology
University of Bristol, Bristol, UK	Postdoc	1995-2002	Behavioral Neuroendocrinology

A. Personal statement

In August, 2007, I was appointed as an Assistant Professor in the Department of Integrative Physiology at the University of Colorado Boulder where I direct the Behavioral Neuroendocrinology Laboratory. My research has led to approximately 99 publications including 64 published or in press, peer-reviewed, original research manuscripts, 26 review or editorial articles, and 9 book chapters. The main focus of my laboratory is investigation of neural mechanisms underlying emotional behavior, with a focus on the role of serotonergic systems.

Environment. The Neuroscience Community at the University of Colorado Boulder is made up of over 80 faculty and research associates in 13 departments and institutes. Neuroscience activities on the campus are coordinated by the Center for Neuroscience. We are fortunate in that there are several research groups within the Center for Neuroscience at CU-Boulder that focus on neural mechanisms underlying responses to stress and adaptation to stress. These include Dr. Serge Campeau (Psychology and Neuroscience), who investigates brain systems involved in perception of stress-related stimuli and the impact of repeated stress on physiological and psychological processes, Dr, Don Cooper (Psychology and Neuroscience and the Institute for Behavioral Genetics), who investigates information processing in the brain motivation/reward memory circuitry and characterizes the adaptations and impaired neural memory mechanisms associated with depression, addiction and schizophrenia, Dr. Heidi Day (Psychology and Neuroscience), who focuses on neural circuitry underlying stress responsiveness, with particular regard to the extended amygdala, Dr. Sona Dimidjian (Psychology & Neuroscience) who investigates depression and the mental health needs of women, Dr. Monika Fleshner (Integrative Physiology), who has a long-standing interest in the role of the dorsal raphe nucleus and serotonergic systems in the resilience-promoting effects of chronic exercise in rodent models, Dr. Benjamin Greenwood (Integrative Physiology), who investigates neurobiological mechanisms underlying the impact of physical activity on stress-related behaviors, including learning and memory, depression, and anxiety in rodents, Tiffany Ito (Psychology & Neuroscience), who investigates affect, attitudes, emotion, and prejudice, integrating psychological and physiological measures, Dr. Kevin Jones (Molecular, Cellular & Developmental Biology) who analyses the role of neurotrophins (nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4/5) in neural development, Dr. Steven Maier (Psychology and Neuroscience), who has a long-standing interest in the role of the dorsal raphe nucleus and serotonergic systems in the anxiety state associated with learned helplessness in rodent models, Dr. Matthew McQueen (Psychology & Neuroscience) who investigates genetic determinants underlying complex disease, with a particular interest in psychiatric, behavioral and neurologic disorders, Dr. Jerry Rudy (Psychology & Neuroscience) who investigates the complementary contributions that the hippocampus and neocortex make to learning and memory, Dr. Robert Spencer (Psychology and Neuroscience), who specializes in stress neurobiology, particularly neuroendocrine mechanisms of stress adaptation, Dr. Tor Wager (Psychology & Neuroscience) who uses fMRI imaging to study brain pathways involved in generating and regulating pain and emotion, and the cognitive and affective mechanisms that implement control, and interventions that include placebo and manipulations of cognitive context, Dr. Linda Watkins (Psychology and Neuroscience), who focuses on neurobiological and psychological impacts of stress-related stimuli, including immune stimuli, and

Dr. Kenneth Wright (Integrative Physiology) who investigates sleep and circadian regulation of human brain function, physiology and behavior. The Stress Research Interest Group meets once a month and the collective experience of these investigators is an invaluable resource for the design, analysis, and interpretation of experiments.

Research Interests. Our laboratory investigates the neural mechanisms underlying emotional behavior and stress-induced regulation of emotional behavior. Our main focus is the role of serotonergic systems in the neuromodulation of physiology and behavior. Current projects address four main topics:

1. *Neural mechanisms underlying anxiety* - identifying the mechanisms underlying regulation of acute and chronic anxiety states, with a focus on developmental influences and interactions among corticotropin-releasing factor (CRF), CRF-related neuropeptides, and serotonergic systems
2. *Effects of peripheral immune activation on serotonergic systems, physiology, and emotional behavior*
3. *Effects of thermal signals on serotonergic systems, physiology, and emotional behavior*
4. *Rapid effects of glucocorticoid hormones* - characterizing the role of corticosterone-sensitive monoamine transporters (organic cation transporters) in regulation of serotonergic systems.

Our laboratory is recognized as one of the leaders in defining, with a high degree of anatomical resolution, subpopulations of serotonergic neurons involved in different stress-related physiological and behavioral responses. Evidence supports anatomically and functionally distinct subpopulations of serotonergic neurons involved in 1) facilitation of anxiety-like responses, 2) inhibition of panic-like responses, 3) regulation of active versus reactive emotional coping responses (including antidepressant-like effects), and 4) regulation of ependymal and cerebrospinal fluid functions. Further characterization of these subsets of serotonergic neurons is likely to lead to novel therapeutic approaches to stress-related psychiatric disease.

Training. Our laboratory is committed to providing the highest quality of research training at the postdoctoral, graduate, undergraduate, and high school level. The University of Colorado Boulder provides an excellent infrastructure for support of research training, including the Undergraduate Research Opportunities Program (UROP)/HHMI, funded by the Biological Sciences Initiative (BSI) through a grant from the Howard Hughes Medical Institute (HHMI), the Bioscience Undergraduate Research Skills and Training (BURST) program, the Ronald E. McNair Postbaccalaureate Achievement Program, and the Colorado Diversity Initiative Summer Multicultural Access to Research Training (SMART) Program. This year, our laboratory is supporting 1 postdoctoral trainee, 4 PhD students, 6 Master's students, 1 professional research assistant (PRAs) as well as a number of undergraduate and high school research projects.

B. Positions and Honors

Positions and Employment

1995-2001	Research Associate, University Research Centre for Neuroendocrinology (URCN), University of Bristol, Bristol, UK
2002-2003	Neuroendocrinology Charitable Trust Research Fellow, Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology (HWLINE), University of Bristol, Bristol, UK
2003-2007	Wellcome Trust Research Career Development Fellowship (RCDF) Research Fellow, HWLINE, University of Bristol, Bristol, UK
2007-present	Assistant Professor, Department of Integrative Physiology and Center for Neuroscience, University of Colorado Boulder, Boulder, CO, USA

Other Experience and Professional Memberships

2010-Present	Member, Endocrine Society
2009-Present	Member, American Physiological Society (APS)
1994-Present	Member, J.B. Johnston Club *An international organization of researchers in comparative and evolutionary neurobiology (Established 1980)*
2003-Present	Member, Psychoneuroimmunology Research Society (PNIRS)
2002-Present	Member, Serotonin Club
1997-Present	Member, Society for Behavioral Neuroendocrinology (SBN)
1992-Present	Member, Society for Neuroscience

Honors

1987	Phi Beta Kappa
1987	Phi Kappa Phi
1983-1987	University of Wyoming Scholars Program
1987	Scottish Rite Foundation of Wyoming, Floyd Holland Memorial Scholarship

1987	Shirley B. Rennard Memorial Scholarship
1987	University of Wyoming Honors
1992-1994	National Institute of Mental Health National Research Service Award (NRSA); Predoctoral Fellowship, *Neural mechanisms of corticotropin-releasing factor*
1994	Rosalind Wulzen-Hugo Krueger Award for Graduate Physiological Research
2002	Winter Conference on Brain Research Travel Fellow
2001-2003	Neuroendocrinology Charitable Trust Fellowship
2003-2006	Wellcome Trust Intermediate Level Research Career Development Fellowship (RCDF) *Integrative physiology and behaviour of anxiety: characterisation of an emotional motor system" and central autonomic control*
2006	Wellcome Trust Value in People Award
2007-2009	2007 NARSAD Young Investigator Award
2009-2014	NSF CAREER Award
2011-2013	2010 NARSAD Young Investigator Award
2011	Anxiety Disorders Association of America Donald F. Klein Early Career Investigator Award

C. Selected peer-reviewed publications

(Selected from approximately 99 original research articles, review articles, and book chapters)

Most relevant to current application (5)

1. Hale MW, Dady KF, Evans AK**, Lowry CA** (2011) Evidence for *in vivo* thermosensitivity of serotonergic neurons in the rat dorsal raphe nucleus and raphe pallidus nucleus implicated in thermoregulatory cooling. Exp Neurol 227: 264-278.
2. **Lowry CA**, Lightman SL, Nutt DJ (2009). That warm fuzzy feeling: brain serotonergic neurons and the regulation of emotion. J Psychopharmacol 23: 392-400.
3. Kelly KJ, Donner NC, Hale MW, **Lowry CA** (2011) Swim stress activates serotonergic and non-serotonergic neurons in specific subdivisions of the rat dorsal raphe nucleus in a temperature-dependent manner, Neuroscience 197:251-268.
4. Jasinka AJ, **Lowry CA**, Burmeister M (2012) Serotonin transporter gene, stress, and raphe-raphe interactions: a molecular mechanism of depression. Trends in Neuroscience (*in press*).
5. **Lowry CA**, Hollis JH, de Vries A, Pan B, Brunet LR, Hunt JRF, Paton JFR, van Kampen E, Knight DM, Evans AK, Rook GAW, Lightman SL (2007) Identification of an immune-responsive mesolimbocortical serotonergic system: potential role in regulation of emotional behavior. Neuroscience 146: 756-772.

Additional recent publications of importance to the field (10)

6. Rook GAW, **Lowry CA** (2008) The hygiene hypothesis and psychiatric disorders, Trends in Immunology, 29: 150-158.
7. Raison CL, **Lowry CA**, Rook GAWR (2010) Inflammation, consternation and sanitation: Loss of contact with co-evolved, tolerogenic micro-organisms and the pathophysiology and treatment of major depression. Archives of General Psychiatry, 67:1211-1224.
8. Hale MW, Stamper CE, Staub DR, **Lowry CA** (2010) Urocortin 2 increases c-Fos expression in serotonergic neurons projecting to the ventricular/periventricular system. Exp Neurol 224: 271-281.
9. Hale MW, **Lowry CA** (2011) Functional topography of midbrain and pontine serotonergic systems: implications for synaptic regulation of serotonergic circuits. Psychopharmacology (Berl). 213:243-264.
10. Rook GAW, **Lowry CA**, Raison CL (2011). Lymphocytes in neuroprotection, cognition and emotion: is intolerance really the answer? Brain, Behav Immun 25: 591-601.
11. Rozeske RR, Evans AK, Frank MG, Watkins LR, **Lowry CA**. Maier SF (2011) Uncontrollable, but not controllable, stress desensitizes 5-HT_{1A} receptors in the dorsal raphe nucleus. J Neurosci 31: 14107-14115.
12. Donner NC, Johnson PL, Fitz SD, Kellen KE, Shekhar A and **Lowry CA** (2012). Elevated *tph2* mRNA expression in a rat model of chronic anxiety. Depress Anxiety 29: 307-319.
13. Hale MW, Rook GAW, Lowry CA (2012) Pathways underlying afferent signaling of bronchopulmonary immune activation to the central nervous system. Chem Immunol Allergy, 98: 118-141.
14. Rook GAW, Raison CL, Lowry CA (2012) Can we vaccinate against depression? Drug Discovery Today, 17: 451-458.
15. Neufeld-Cohen A, Kelly PA, Paul ED, Carter RN, Skinner E, Olverman HJ, Vaughan JM, Issler O, Kuperman Y, **Lowry CA**, Vale WW, Seckl JR, Chen A, Jamieson PM. Chronic activation of

corticotropin-releasing factor type 2 receptors reveals a key role for 5-HT_{1A} receptor responsiveness in mediating behavioral and serotonergic responses to stressful challenge. Biol Psychiatry, in press.

D. Research Support

Ongoing Research Support

NSF CAREER Award (NSF-IOS 0845550) 02/01/09–01/31/14
Afferent thermosensory mechanisms and social behavior
This project will investigate afferent thermal signaling mechanisms regulating serotonergic systems and emotional behavior.
Role: PI

National Institute of Mental Health (2R01 MH065702) 07/10/09–06/30/14
Role of serotonin and CRF pathways in anxiety and HPA regulation
This study will investigate the forebrain and brainstem neural systems (including serotonergic systems) underlying acute and chronic anxiety states.
Role: PI (Multiple PI proposal with Anantha Shekhar)

NSF Project Grant (NSF-IOS 0921969; 1 year no-cost extension until 07/31/13 08/01/09–07/31/12
Collaborative Research: Novel corticosteroid actions on neurotransmitter function
This project will investigate neural mechanisms underlying rapid actions of corticosterone in the rat dorsomedial hypothalamus to regulate organic cation transporter 3 (OCT3) activity and hypothalamic-pituitary-adrenal (HPA) axis activity.
Role: PI (Multiple PI proposal with Miles Orchinik and Kenneth Renner)

National Institute of Mental Health (R01 MH086539) 09/08/09–06/30/13
Mechanisms underlying stress-induced activation of serotonergic systems
This study will investigate the neuroendocrine and neural mechanisms underlying stress-induced activation of serotonergic systems, focusing on amygdala-dorsal raphe nucleus pathways.
Role: PI

NARSAD (2010 Young Investigator Award) 01/15/11−01/14/13
Evaluation of tryptophan hydroxylase 2 expression in bipolar depressed patients.
This study will investigate expression of tryptophan hydroxylase 2 protein expression in the midbrain raphe complex of postmortem brain tissue from bipolar depressed patients and controls.
Role: PI

National Institute of Drug Abuse (R01) 07/01/11–06/30/16
Neural sensitivity to stress during drug withdrawal
This project will investigate the interaction between CRF and serotonin, and how drugs of abuse such as amphetamine alter this interaction to increase anxiety states during drug withdrawal.
Role: Co-investigator (PI, Dr. Gina Forster)

National Institute of Mental Health (R01) 07/01/11–06/30/13
Glucocorticoid negative feedback: intrinsic and extrinsic mechanisms
This study will investigate neural mechanisms underlying rapid negative feedback control of the hypothalamic-pituitary-adrenal (HPA) axis, focusing on negative feedback at the level of the paraventricular nucleus of the hypothalamus (PVN) and pituitary.
Role: Co-investigator (PI, Dr. Robert Spencer)

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Matthias R. Mehl	Associate Professor of Psychology Adjunct Associate Professor of Communication Associate Investigator at the Arizona Cancer Center
eRA COMMONS USER NAME mehlmr	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Erlangen, Germany	B.A. / M.A.	1998	Psychology
University of Texas, Austin	Ph.D.	2004	Psychology

A. Personal Statement

My role in this project is to oversee all aspects around the measurement and statistical controlling of social and emotional processes during Whole Body Hyperthermia (WBH) treatment. My primary responsibilities will be (a) to optimize the assessment of WBH-related social and emotional disclosure processes, (b) to propose statistical ways to remove their impact on the primary study outcomes. As a trained social and health psychologist, I have extensive expertise in the behavioral assessment of emotional and social processes in interpersonal interactions. I joined the faculty of the Psychology Department of the University of Arizona in 2004 where I am now a tenured Associate Professor. I am also an Adjunct Associate Professor in the Department of Communication and an Associate Investigator at the Arizona Cancer Center. Finally, I am the Vice President of the Society for Ambulatory Assessment, an international scientific organization dedicated to foster research in everyday life and a board member of the Association for Research in Personality. My prior research has been published in various high impact journals (incl. *Science, Psychological Science, Journal of Personality and Social Psychology, Psychological Assessment, and Health Psychology*) and has been funded, among other sources, by the American Cancer Society and the NIH (NCI, NCCAM).

B. Positions and Honors

Employment

09/98 to 07/99	Visiting Scholar, Department of Psychology, University of Texas at Austin.
10/99 to 03/00	Research Assistant, Institute for Physiological Psychology, University of Düsseldorf
01/01 to 08/03	Research Assistant, Department of Psychology, University of Texas at Austin
08/03 to 05/04	Teaching Assistant at the University of Texas at Austin
08/04 to 06/10	Assistant Professor, Department of Psychology, University of Arizona
01/07 to 06/10	Adjunct Assistant Professor, Department of Communication, University of Arizona
01/07 to present	Associate Investigator, Arizona Cancer Center, University of Arizona
07/10 to present	Adjunct Associate Professor, Department of Communication, University of Arizona
07/10 to present	Associate Professor, Department of Psychology, University of Arizona
10/11 to present	Affiliate Faculty, Evelyn F. McKnight Brain Institute, University of Arizona

Honors and Awards

12/96 to 07/98	Undergraduate Fellowship of the 'Studienstiftung des deutschen Volkes' (German National Academic Foundation).
09/98 to 07/99	Postgraduate Research Fellowship of the 'Studienstiftung des deutschen Volkes' (German National Academic Foundation) for studying abroad
01/02	Student Travel Award of the Society for Personality and Social Psychology
09/03 to 05/04	University Continuing Fellowship, University of Texas at Austin
08/06	Young Investigator Travel Award of the Deutsche Forschungsgemeinschaft [German Research Foundation] for traveling to a conference in Germany
05/07	Social and Behavioral Sciences Research Institute Faculty Summer Research Grant Development Award, University of Arizona
05/07	Foreign Travel Grant, Office of International Affairs, University of Arizona
01/08	Listed in *Dialogue*, the Society for Personality and Social Psychology's newsletter, as one of the ten most cited Assistant Professors in Social/Personality Psychology
05/11	Identified as a Rising Star by the Association for Psychological Science (Rising Star Profile in the May/June Issue of the Observer)

C. Selected Peer-reviewed Publications (Selected from 39 peer-reviewed publications)

Most relevant to the current application

1. Mehl, M. R., Pennebaker, J. W., Crow, M. D., Dabbs, J., & Price, J. H. (2001). The Electronically Activated Recorder (EAR): A device for sampling naturalistic daily activities and conversations. Behavior Research Methods, Instruments, and Computers, 33, 517–523.
2. Mehl, M. R., Vazire, S., Ramírez-Esparza, N., Slatcher, R. B., & Pennebaker, J. W. (2007). Are women really more talkative than men? Science, 317, 82.
3. Mehl, M. R., & Holleran, S. E. (2007). An empirical analysis of the obtrusiveness of and participants' compliance with the Electronically Activated Recorder (EAR). European Journal of Psychological Assessment, 23, 248-257.
4. Mehl, M. R., Vazire, S., Holleran, S. E., & Clark, C. S. (2010). Eavesdropping on happiness: Well-being is related to having less small talk and more substantive conversations. Psychological Science, 21, 539-541. PMCID: PMC2861779
5. Mehl, M. R., Robbins, M. L., & Deters, g. F. (2012). Naturalistic observation of health-relevant social processes: The Electronically Activated Recorder (EAR) methodology in psychosomatics. Psychosomatic Medicine, 74, 410-417.

Additional recent publications of importance to the field (in chronological order)

1. Pennebaker, J. W., Mehl, M. R., Niederhoffer, K. (2003). Psychological aspects of natural language use: Our words, our selves. Annual Review of Psychology, 54, 547–577.
2. Mehl, M. R., & Pennebaker, J. W. (2003). The sounds of social life: A psychometric analysis of students' daily social environments and natural conversations. Journal of Personality and Social Psychology, 84, 857-870.
3. Mehl, M. R., & Pennebaker, J. W. (2003). The social dynamics of a cultural upheaval: Social interactions surrounding September 11, 2001. Psychological Science, 14, 579-585.
4. Mehl, M. R., Gosling, S. D., & Pennebaker, J. W. (2006). Personality in its natural habitat: Manifestations and implicit folk theories of personality in daily life. Journal of Personality and Social Psychology, 90, 862–877.

5. Mehl, M. R. (2006). The lay assessment of sub-clinical depression in daily life. Psychological Assessment, 18, 340-345.
6. Rohrbaugh, M. J., Mehl, M. R., Shoham, V., Reilly, E., & Ewy, G. A. (2008). Prognostic significance of spouse *we* talk in couples coping with heart failure. Journal of Consulting and Clinical Psychology, 76, 781-789.
7. Vazire, S., & Mehl, M. R. (2008). Knowing me, knowing you: The relative accuracy and unique predictive validity of self- and other ratings of daily behavior. Journal of Personality and Social Psychology, 95, 1202-1216.
8. Ramírez-Esparza, N., Mehl, M. R., Álvarez Bermúdez, J., & Pennebaker, J. W. (2009). Are Mexicans more or less sociable than Americans? Insights from a naturalistic observation study. Journal of Research in Personality, 43, 1-7.
9. Holtzman, N. S., Vazire, S., & Mehl, M. R. (2010). Sounds like a narcissist: Behavioral manifestations of narcissism in everyday life. Journal of Research in Personality, 44, 478-484. PMCID: PMC2918908
10. Robbins, M. L., Mehl, M. R., Holleran, S. E., & Kasle, S. (2011). Naturalistically observed sighing and depression in rheumatoid arthritis patients: A preliminary study. Health Psychology, 30, 129-133.

D. Research support

Ongoing Research Support

3R01AT004698-01A1S1 Raison (PI) 09/30/09 to 09/29/12
Mechanisms of Meditation
The main goal of this project is to use a novel naturalistic observation method (the Electronically Activated Recorder or EAR) to examine whether meditation training changes participants' real-world, prosocial and affiliative behavior.
Role: Co-investigator

1 R01AT007297-01 Raison (PI) 09/30/2011 to 06/30/2015
Inflammation, Stress, and Social Behavior: Using Ecological Assessments and Model Systems
The goal of this project is to examine the relationships among social interactional processes, inflammation, and stress reactivity and to identify behavioral and physiological mechanisms through which Positive Social Connectivity and Negative Social Processes interact with psychosocial stress to promote resilience in the context of illness.
Role: Co-Investigator

1R01HD069498-01 Bootzin (PI) 8/19/11 to 04/30/15
Sleep and Divorce: Identifying Bidirectional Vulnerability and Resilience
The goal of this project is to collect sleep, social engagement, distress data from recently separated individuals in a longitudinal study to improve our understanding of why some people are at elevated risk for poor health outcomes following relationship dissolution.
Role: Co-Investigator

John Templeton Foundation/ WFU Mehl (PI) 8/1/11 to 06/15/2013
Eavesdropping on Character: Testing the Stability, Variability, and Changeability of Naturalistically Observed Virtuous Daily Behavior
The goal of this project is to use a novel naturalistic observation method (the Electronically Activated Recorder or EAR) to test how stable, variable, and changeable virtuous behavior is in daily life.
Role: PI

Completed Research Support

American Cancer Society IRG-74-001-28 Mehl (PI) 01/01/2007-12/312007

Coping in Inter-(action): A Naturalistic Observation Approach to Studying Couples Coping with Breast Cancer,
The goal of this project was to pilot test a novel naturalistic observation method (the Electronically Activated Recorder or EAR) in a sample of recently diagnosed breast cancer patients and their partners.
Role: PI

Vice President of Research Faculty Small Grant Mehl (PI) 05/01/2005 – 04/30/07
Pilot Test of a Method for Studying Coping in Real-time
The goal of this project was to pilot test a novel naturalistic observation method (the Electronically Activated Recorder or EAR) in a sample of Rheumatoid Arthritis patients.
Role: PI

1R03CA137975-01A1 Mehl (PI) 07/01/09 to 06/30/12
The Daily Interactions of Couples Coping with Breast Cancer: With Whom, About What, and Links to Adjustment
The goal of this project is to use a novel naturalistic observation method (the Electronically Activated Recorder or EAR) to examine with whom and about what couples coping with breast cancer talk in their real-world interactions and how differences in what patients and partners talk about relate to adjustment.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Thienhaus, Ole J.	Professor and Chair, Department of Psychiatry, University of Arizona College of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Freiburg, Germany		1974	Pre-med
Free University of Berlin, Germany	M.D.	1978	Medicine
University of Cincinnati	M.B.A.	1985	Business

A. Positions and Honors

2012-	Professor and Chairman, Department of Psychiatry University of Arizona College of Medicine
1996-2012	Professor and Chairman, Department of Psychiatry and Behavioral Sciences, University of Nevada School of Medicine
1996-	President, University Mental Health Professionals, Inc. of MEDSchool Associates of the University of Nevada School of Medicine
1996-	Board of Trustees, MedSchool Associates of the University of Nevada School of Medicine
1993-1994	President of Faculty Forum, University of Cincinnati
1993-1995	Chief Clinical Officer, University Hospital Cincinnati
1992-1995	Trustee, Board of Trustees Southwestern Ohio Seniors' Services, Inc.
1991-1995	Associate Professor of Emergency Medicine (Joint Appt.) University of Cincinnati, College of Medicine
1991-1995	Director, Psychiatric Emergency Service, University of Cincinnati Medical Center
1990-1995	Vice chair, Department of Psychiatry, University of Cincinnati
since 1989	Ad hoc member of Special Review Board National Institute of Mental Health - Aging Branch, and National Institutes of Health NCCAM
1989-1995	Trustee and Treasurer, Board of Trustees, Professional Psychiatric Services, Inc., Cincinnati
1988-1995	Associate Professor of Psychiatry, University of Cincinnati
1988-1989	Consultant Surveyor for the Joint Commission on Accreditation of Health Care Organizations
1985-1988	Assistant Professor of Psychiatry, University of Cincinnati
1985-1991	Attending Physician, Geropsychiatry, Inpatient Unit at University Hospital
1985-1995	Psychiatric Consultant to Cincinnati V.A. Medical Center
1985-1991	Consultant to Comprehensive Care Center of Northern Kentucky
1984-1990	Psychiatric Consultant to Cincinnati Area Senior Services
1984-1995	Attending Psychiatrist, Psychiatric Emergency Service, University of Cincinnati Hospital
1983-1984	Clinical Fellow in Geriatric Psychiatry, University of Cincinnati, Department of Psychiatry
1980-1983	Resident in Psychiatry, University of Cincinnati, Department of Psychiatry

1979-1980	Neurosurgical House Officer, Municipal Hospital Neukölln, West Berlin, Germany
1978-1979	Junior House Officer in General Surgery, Evangelisch-Lutherische Diakonissenanstalt (Lutheran City Hospital), Flensburg, Germany
1972-1978	Fellow of the German National Scholarship Foundation (Studienstiftung des deutschen Volkes)
1981	Doctorate of the Albert-Ludwigs-University, Freiburg, Germany, Forensic Pathology: Doktor der Medizin
1994	Fellow of the American Psychiatric Association
2002	Fellow American College of Psychiatrists
2003	Distinguished Fellow of the American Psychiatric Association

B. Selected publications (in chronological order, out of about 100).

1. Thienhaus OJ, Hartford JT: Alcoholism in the elderly. Psychiatric Medicine 1984; 2:27-41
2. Thienhaus OJ, Khosla N: Meningeal cryptococcosis misdiagnosed as a manic episode. American Journal of Psychiatry 1984;141:1459-1460
3. Bosmann HB, Thienhaus OJ: Research in geriatric psychiatry: a view from the United States. Social Psychiatry 1985; 20:1-4
4. Thienhaus OJ, Skelly MF, Hartford JT, Bosmann HB: Biological markers in Alzheimer's disease. Journal of the American Geriatrics Society 1985; 35:715-726
5. Thienhaus OJ, Hartford JT: Depression in hyperprolactinemia. Psychosomatics 1986; 27:663-664
6. Thienhaus OJ, Conter L, Bosmann HB: Sexuality and aging. Aging and Society 1986; 6:39-54
7. Thienhaus OJ, Cliffe C, Zemlan FP, Bosmann HB: Superoxide dismutase, chromosome 21, and Alzheimer's disease. Biological Psychiatry 1986; 21:1106-1107
8. Thienhaus OJ, Wheeler BG, Simon S, Zemlan FP, Hartford JT: A controlled double-blind study of high dose dihydroergotoxin mesylate (Hydergine) in mild dementia. Journal of the American Geriatrics Society 1987; 35:219-223
9. Thienhaus OJ, Zemlan FP, Bienenfeld D, Hartford JT, Bosmann HB: Growth hormone response to edrophonium in Alzheimer's disease. American Journal of Psychiatry 1987; 144:1049-1052
10. Thienhaus OJ: Impact of shortened hospitalization on outcome parameters. European Archives of Psychiatry and Neurological Sciences 1987; 236:299-302
11. Thienhaus OJ: A practical overview of sexual function and advancing age. Geriatrics 1988; 43(8):63-68
12. Thienhaus OJ, Rowe C, Woellert P, Hillard JR: Geropsychiatric emergency service: utilization and outcome predictors. Hospital and Community Psychiatry 1988; 39:1301-1305
13. Zemlan FP, Thienhaus OJ, Bosmann HB: Superoxide dismutase activity in

Alzheimer's disease: possible mechanism for paired helical filament formation. Brain Research 1989; 476:162-165

14. Thienhaus OJ: Depression in the elderly: phenomenology and pharmacotherapy. Geriatric Medicine Today 1989; 8:34-45 (invited paper)
15. Thienhaus OJ, Margletta S, Bennett JA: A study of the clinical efficacy of maintenance ECT. Journal of Clinical Psychiatry 1990; 51:141-145
16. Zemlan FP, Thienhaus OJ, Garver DL: Length of psychiatric hospitalization and prediction of antipsychotic response. Progress in Neuropsychopharmacology and Biological Psychiatry 1990; 14:13-24
17. Thienhaus OJ, Thoene J, Allen A, Zemlan FP: Anticholinergische Plasmaaktivität und kognitive Funktion bei geriatrischen Patienten. Psychiatrie, Neurologie und Medizinische Psychologie 1990; 42:275-281 (English abstract)
18. Thienhaus OJ, Allen A, Bennett JA, Chopra YM, Zemlan FP: Anticholinergic serum levels and cognitive performance. European Archives of Psychiatry and Neurological Sciences 1990; 240:28-33
19. Sinha D, Zemlan FP, Nelson S, Bienenfeld D, Thienhaus O, Hamilton S: A new scale for assessing behavioral agitation in dementia. Psychiatry Research 1992;41:73-88
20. Thienhaus OJ: Antidepressive Pharmakotherapie in der Geriatrie. Deutsches Ärzteblatt (Journal of the German Medical Association) 1992;89:2550-2555
21. Stein L, Thienhaus OJ: Hearing loss and psychosis. International Psychogeriatrics 1993;5:49-57
22. Schuster JM, Thienhaus OJ, Fogel B, Restak R, Tucker G: Cost-effective care of neuropsychiatric inpatients. J Neuropsychiatry Clin Neurosci 1995;7:1-5
23. Thienhaus OJ: Pitfalls in presenting and interpreting clinical trial data. Psychopharmacology Bulletin 1995;31:435-438
24. Piasecki M, Steinagel G, Thienhaus OJ, Kohlenberg BS: An exploratory study: The use of paroxetine for methamphetamine craving. Journal of Psychoactive Drugs 2002;34:301-304
25. Thienhaus OJ, Piasecki M: Assessment of geriatric patients in the psychiatric emergency service. Psychiatric Services 2004;55:639-640
26. Thienhaus OJ: The AMA health insurance proposal (letter). JAMA 2004;292:1173
27. Hunt T, Thienhaus OJ, Ellwood A: The mirror lies: body dysmorphic disorder (in press). American Family Physician 2007

Book Chapters

28. Hartford JT, Thienhaus OJ: Psychiatric aspects of alcoholism in the elderly. In: Alcoholism in Old Age: Social and Biomedical Issues. Edited by Hartford JT, Samorajski T. New York, Raven, 1984 (pp. 253-262)
29. Thienhaus OJ, Hartford JT: The elderly alcoholic: considerations for the primary care physician. In: Second Geriatric Medicine Annual 1987. Edited by Ham RJ. Oradell, NJ, Medical Economics Books, 1987 (pp. 160-172)

FACILITIES

Clinical/Translational Research Facilities

The Department of Psychiatry at the University of Arizona College of Medicine in Tucson, Arizona, is the only academic department of psychiatry in Arizona. The department has more than 40 full-time faculty members, 44 psychiatric residents, 5 child and adolescent psychiatry fellows, and 4 clinical psychology interns. In addition to the general community, there are two major affiliated hospital systems in Tucson from which research participants may be recruited, including the University of Arizona Medical Center (University and South Campuses) and the Southern Arizona Veterans Administration Health Care System. This includes inpatient and outpatient facilities of the Community Partnership of Southern Arizona, the administrative organization responsible for the coordination of publicly-funded behavioral health treatment and prevention services in southern Arizona. Our Outpatient Clinic on University Campus occupies about 6,000 square feet with 32 exam rooms and access to Clinical and Translational Sciences (CaTS) Research Center facilities (described below). The University Campus has approximately 10,000 psychiatry visits per year. Patients are frequently referred by community physicians who are aware of the department's ongoing commitment to research on mood disorders. The South Campus Outpatient Clinic occupies 2,650 square feet with 23 exam rooms/physician offices and has nearly 5,000 patient visits per year with significant growth this past year due to the new Behavioral Health Pavilion that was completed in 2011.

The Department of Psychiatry has an active research program with staff devoted to research administration, including a director, operations manager, and research specialists. All have experience with IRB/regulatory matters and grants administration. Business office staff are knowledgeable in grants finance and accounting, and work-study students devoted to research are available for data entry and other administrative support. The Department provides Dr. Raison with office space in the Arizona Health Sciences Center, and he maintains an office through his joint appointment at the Norton School of Family and Consumer Science at McClelland Park as well. Additional office and administrative space is available for study staff in the Department of Psychiatry Research suites. Through Dr. Raison's joint appointment to the Norton School of Family and Consumer Sciences, he has access to the Lang Family Observation Laboratory, a state-of-the-art lab designed for the collection of audio, visual, physiological data (EKG, impedance cardiography, respiration, blood pressure, skin conductance, and pulse amplitude) in studies of couple, group, and family interaction. The Lang Lab offers three subject rooms, one classroom, two control rooms, one-way mirrors, and video and sound capabilities.

To be used for participant visits for the current proposal at the University of Arizona, the Clinical and Translational Sciences (CaTS) Research Center occupies 3,700 square feet and is adjacent to the University of Arizona Medical Center and College of Medicine, which allows convenient use of hospital resources including clinical laboratories and other clinical departments. It provides six private exam rooms as well as a room for private intravenous infusions. It also houses a larger multi-subject study room with 7 infusion chairs. There are 3 interview rooms, 2 pediatric observation rooms, a reception/waiting area, 2 conference rooms, 2 sample processing/storage rooms and a room for taking vital signs and performing ECGs. Staffing consists of 3 full-time Coordinators, a full-time Registered Nurse and a Bioinformatics Manager. Similar to the Psychiatry research personnel, CaTS staff are trained in human subject research through the Collaborative Institutional Training Initiative (CITI) program, and they receive HIPAA and Good Clinical Practice Guidelines training. The Center's lab equipment includes two -20° freezers, refrigerators, one -80°C freezer, 2 centrifuges (including a refrigerated centrifuge), automated blood pressure machines, an ECG machine and a defibrillator. The facilities and equipment are routinely inspected and maintained. The Center is covered by the University of Arizona Medical Center's code blue emergency system. The Heckel HT3000 system that will be used for both hyperthermic and sham treatments for the current application is currently housed in CaTS in a dedicated room.

Computer

The home department of the PI, the Department of Psychiatry, provides personal computer resources for word processing, email transmission, internet access, and statistical analysis software for all staff, as well as laser printers, fax machines, scanners and photocopy machines. In addition to these resources, the University of Arizona maintains full computer and data analytic processing components available to all university faculty on a fiber-optic network system, with automatic daily backup available on a secure server.

Research Electronic Data Capture (REDCAP) is a secure, web-based application designed to support data capture for studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data and

export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. This application will be used in the development of electronic forms for data collection to be used by study staff in screening and seeing subjects in CaTS for study visits on encrypted, secure laptops and saved to a secure network, backed up nightly.

Equipment

The Heckel HT3000 whole-body hyperthermia system (Heckel Medizintechnik GmbH, Esslingen, Germany, and Hydrosun Medizintechnik GmbH, Mullheim, Germany) is a joint development of two companies with expertise in specialized technology and research on water-filtered infrared-A (wIRA) heat radiation combined with whole-body hyperthermia to penetrate into deeper-lying tissues to allow application of wIRA at higher intensities. The system includes patient monitoring (temperature, EKG, SPO2, NIBP, RESP) and software. Through a grant from the Braun Foundation, the University of Arizona has received the machine on loan specifically for this research study with a non-significant risk device determination from our local IRB. This loan includes use of the machine along with a medical computer with screen and FebroData software; no cost will be applied to the grant for this equipment. This system has been installed and housed in the CaTS Research Center for use only with study visits in this protocol. Our research program also maintains 1) a supply of Philips Respironics Actiwatch-2 and docking stations with sleep/wake recording activity and ambient light monitoring; and 2) Equivital wireless monitoring system for core body temperature.

Behavioral Neuroendocrinology Laboratory

Dr. Lowry's laboratory at the University of Colorado- Boulder has all equipment necessary for conducting and documenting results for immunohistochemistry, immunofluorescence, and *in situ* hybridization histochemistry, including an image analysis system for quantification of autoradiographic films (Qimaging, Surrey, BC, Canada). A Thermo Scientific Multiskan® EX 96-well plate reader (Thermo Fisher Scientific Inc., Waltham, MA) is available for ELISA assays of plasma BDNF, and cytokine concentrations A –80 °C freezer (Thermo Fisher Scientific, Inc.) and multiple –20 freezers and refrigerators are available to store reagents and tissue samples.

Other

Dr. Raison is member of the Mechanisms of Emotion, Social Regulation, and Health (MESH) Collaborative at the University of Arizona. MESH is an interdisciplinary and translational collaborative of investigators with funded studies on the neurobiological basis of depressive disorders and the impact of depression on related social-emotional processes. The collaborative meets monthly and includes members of the Departments of Psychiatry, Psychology, and Human Studies and Family Development.

Image 1. Image of Heckel HT3000

Image 2. Close-up of Heckel HT3000

Foundation Budget Request
University of Arizona - Charles Raison, MD
November 1, 2012 - October 31, 2014

No. Subjects 30

	Year 1 2012/13	Year 2 2013/14	TOTAL
Consultants:			
Kay Hanusch	$ 1,500	$ 1,500	$ 3,000
Total Consultants:	**$ 1,500**	**$ 1,500**	**$ 3,000**
Other Expenses:			
Subject fees - $400 each	$ 6,000	$ 6,000	$ 12,000
Research supplies	$ 1,500	$ 562	$ 2,062
SCID-I Research Version (SCID-I-RV)	$ 50	$ -	$ 50
REDCap Forms Development	$ 500		$ 500
Recruitment/Advertising	$ -	$ -	$ -
CATS Services (ECG, Blood Draws/Processing, Exam Rooms, etc.)	$ 10,000	$ 10,000	$ 20,000
Lab Supplies	$ 600	$ 600	$ 1,200
Screening Labs	$ 1,500	$ 1,500	$ 3,000
Assays (BDNF and cytokines)	$ 2,248	$ -	$ 2,248
Total Other Expenses:	**$ 22,398**	**$ 18,662**	**$ 41,060**
Subcontract: UC-Boulder			
Christopher Lowry, PhD - Avg 2% effort $ 103,083 27.5% fringe	**$ 2,830**	**$ 3,109**	**$ 5,940**
Subtotal Direct Costs:	**$ 26,728**	**$ 23,271**	**$ 50,000**
Indirect Costs - 10% allowed	**$ 2,673**	**$ 2,327**	**$ 5,000**
Total:	**$ 29,401**	**$ 25,598**	**$ 55,000**

BUDGET JUSTIFICATION

Personnel:
Charles Raison, MD, (Principal Investigator) is an Associate Professor of Psychiatry and the Barry and Janet Lang Associate Professor of Integrative Mental Health at the Norton School of Family and Consumer Sciences (NSFCS) at the University of Arizona. Dr. Raison will oversee all aspects of the study, including consulting with co-investigators, subject recruitment/screening/psychiatric evaluation, acquisition and analysis of behavioral/psychosocial and biological data, day-to-day administration of the project, oversight of data security, writing of progress reports and communication with sponsor, and data analysis and reporting of findings. Dr. Raison has 10% protected time (1.2 calendar months) reserved for innovative research on this project.

Matthias Mehl, PhD, (Co-investigator) is an Associate Professor of Psychology at the University of Arizona. Dr. Mehl will be responsible for input on the standardization of study staff-participant interactions during WBH and sham sessions, and input on the design for transcribing audiotaped treatment sessions. Dr. Mehl will devote 1% academic year effort on this project funded by the Department of Psychology.

Ole J. Thienhaus, MD, (Co-investigator) is a Professor and Chair of the Department of Psychiatry at University of Arizona. Dr. Thienhaus will work with Dr. Raison regarding participant safety during WBH and sham procedures, and in terms of risks inherent in subject population, e.g., depression, suicide. Dr. Thienhaus will devote 1% effort (0.12 calendar months) on this project funded by the Department of Psychiatry.

Equipment: The Heckel HT3000 whole body hyperthermia device that will be used for the current project has been loaned free of charge to the University of Arizona for this study. The device has received non-significant risk device determination status from our IRB, cleared customs, and is presently installed in the CaTS research clinic.

Funding Needs Reflected in Foundation Budget: The framework has been laid, but this innovative and novel pilot study cannot proceed without additional funds to cover operating costs associated with the recruitment, enrollment and participation of subjects. This research is unlikely to be funded through other major peer-reviewed mechanisms. This budget does not include duplication of other funding or a reduction in funding from another source. ***Costs requested through this Foundation grant are as follows:***

Consultant: Kay Hanusch has extensive experience in the use of the device for the treatment of major depression in medically healthy adults in the European Union. He will train study personnel in use of equipment and application of clinical protocol for treating depression with hyperthermia ($1,500 each year; $3,000 total).

Subaward: Christopher A. Lowry, PhD, (Co-investigator) is an Assistant Professor in the Department of Integrative Physiology and Center for Neuroscience at the University of Colorado, Boulder. As co-investigator, Dr. Lowry will conduct baseline and follow-up measurements of plasma concentrations of brain-derived neurotrophic factor (BDNF), interleukin 6 (IL-6), IL-1β, tumor necrosis factor alpha (TNFα) and IL-10. We are requesting support for 2% effort for both project years, for a total of $5,940.

Supplies: Research supplies specific to the project including core body temperature monitoring pills, sleep diaries, and device-specific cleaning/disinfection supplies between subjects will total $2,062. The SCID-I Research Form for subject assessments will cost $50 in Year 1. ELISA kits for BDNF, IL-1beta, IL-6, TNFalpha, and IL-10 are quoted at $2,248 in Year 1. Lab supplies to collect bloodwork for screening and iodine tabs for sweat gland analysis will be $600 in each year; $1200 total. Screening labs are $100 each or $3,000 total.

Subject-related expenses: Subject fees at $400 each for 30 subjects, $6,000 in each year or $12,000 total.

Other expenses: REDCAP online data capture forms development, $500 in Year 1. CaTS Research Clinic Fee for Service including ECGs, blood draws/processing/shipping, exam room space, $10,000 in each year; $20,000 total.

Total Direct Costs: $50,000
Allowable Indirect: $5,000
Total Funds Requested: $55,000

University of Colorado Boulder

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6 August, 2012

Charles L. Raison, MD
Associate Professor
Department of Psychiatry
College of Medicine
Barry and Janet Lang Associate Professor
John and Doris Norton School of Family and Consumer Sciences
1501 N. Campbell Ave
Box 245002
Suite 7303B
Tucson, AZ 85724
Email: craison@email.arizona.edu

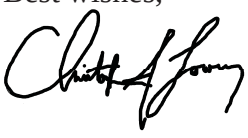
Dear Dr. Raison,

This letter is to convey my unequivocal and enthusiastic support for your Depressive and Bipolar Disorder Alternative Treatment Foundation (DBDAT) proposal to determine the effects of whole-body heating (WBH) on depressive symptoms in patients with major depressive disorder (MDD). Your preliminary data, showing antidepressant effects of a single treatment with WBH in an open trial using mild, short-duration WBH is extremely exciting and warrants further study. In my own studies in rodents, we have shown that exposure to warm temperature activates subpopulations of brain serotonergic neurons implicated in anxiolytic and antidepressant-like behavioral responses, providing a potential mechanistic explanation for the antidepressant effects of WBH in humans. I look forward to collaborating on your exciting studies using WBH in patients with MDD. Specifically, I agree to conduct measurements, at baseline and following treatment with WBH or sham-WBH, of plasma concentrations of brain-derived neurotrophic factor (BDNF), interleukin 6 (IL-6), IL-1β, tumor necrosis factor alpha (TNFα) and IL-10 in an attempt to begin to understand physiological responses to WBH in humans, an important first step in understanding potential mechanisms.

My involvement in your proposal will expedite our shared interests by providing data from our upcoming rodent studies related to identifying biomarkers of warming, as well as biomarkers that might be linked to antidepressant effects. I wish you luck on your application. I firmly believe that your proposed studies have the potential to be transformational in the approach to treatment of MDD.

Please do not hesitate to contact me should you have any questions.

Best wishes,



Christopher A. Lowry

THE UNIVERSITY OF ARIZONA

Matthias R. Mehl, Ph.D.
Department of Psychology
College of Science
School of Mind, Brain & Behavior

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August 9, 2012

Charles L. Raison, M.D.
1501 N. Campbell Ave
Box 245002
Tucson AZ 85724

Dear Dr. Raison:

I would be delighted to serve as a Co-Investigator on your project *Whole Body Hyperthermia & Major Depression (MDD)*.

I fully support your proposal to conduct a randomized, placebo controlled, clinical trial to determine if Whole Body Hyperthermia (WBH) has antidepressant effects. You have proposed a highly innovative study that will have both important implications for both understanding and treating depression.

This proposal is related to my work on the role that psychosocial processes play in coping with stress and depression. As part of the grant, I am ready to lend my expertise to measuring and statistically controlling social and emotional processes that may be elicited during the WBH treatment (i.e., while participants are in the Heckel device) to detect, with the highest degree of fidelity, the direct effect of hyperthermia treatment..

Again, this is an exciting project that I am delighted to be part of. I very much look forward to our collaboration!

Sincerely,

Matthias Mehl, Ph.D.
Associate Professor, Department of Psychology
Adjunct Associate Professor, Department of Communication
Associate Investigator, Arizona Cancer Center
Affiliate Faculty, Evelyn F. McKnight Brain Institute

THE UNIVERSITY OF ARIZONA
HEALTH NETWORK

Ole J. Thienhaus, M.D.
Professor and Head
Department of Psychiatry

17 August 2012

Charles Raison, M.D.
Associate Professor
Department of Psychiatry
University of Arizona
1501 N. Campbell Avenue
Tucson, AZ 85724-5002

Dear Dr. Raison,

I am enthused to serve as a co-investigator on your grant application to The Depressive and Bipolar Disorder Alternative Treatment Foundation for the project entitled *Whole Body Hyperthermia & Major Depression (MDD).* This project is remarkable in its combination of clinical relevance and potential for uncovering novel pathogenic mechanisms for depression based on a true "mind-body" perspective. This project, as you know, is foundational to our developing Center of Excellence for Emotional Health in the Department of Psychiatry, so--given my chairmanship--I have an interest in this work that transcends my role as co-investigator. As co-investigator, I will aid you in both administrative and clinical aspects of the work.

Again, I look forward to collaborating with you on this exciting project.

Sincerely,

Ole J. Thienhaus, M.D.

1501 N. Campbell Avenue · P.O. Box 5002 · Tucson, Arizona 85724
2800 East Ajo Way · Behavioral Health Pavilion · Tucson, Arizona 85713

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August 15. 2012

RE: Consulting for whole body hyperthermia and major depression.

I will be delighted to serve as a consultant for your application that seeks to examine the potential of hyperthermia as a treatment for major depression. As you know I have significant experience with the clinical use of hyperthermia for the treatment of depression in my clinic in Switzerland. I also have expertise with the Heckel HT3000 that will be used in your study. As a consultant I will plan to spend sufficient time at the study site to train study personal on the use of the system in depressed subjects. I will also be able to provided tutorials on basic aspects of machine calibration, troubleshooting, etc. In addition to my time in the U.S., I will be available to discuss both technical and clinical questions that might arise as the study proceeds.

I look forward to participating in this exciting and remarkably innovative project.

Sincerely

Aeskulap-Klinik

Kay-u. Hanusch

dipl. Physiotherapist for advanced physiotherapy HF
Therapist for clinical psycho-neuro-immunology
Heat of physiotherapy

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