MEDITATION AND DEPRESSION

by

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DEDICATION

To my parents,

Peter Price Britton and Beatrice Willoughby Totten Britton

for their undying support, enthusiasm and generosity.

To Sarah McKnight Devens,

November 17th 1973 - July 10, 1995

Whose death reminds us all of the urgency of this research

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ABSTRACT

Although meditation-based interventions have been associated with improvement in depressive symptoms and prevention of relapse, the physiological mechanisms of meditation's therapeutic effects are unknown. At the same time, a growing body of literature has shown that meditation has profound effects on numerous physiological systems that are involved in the pathophysiology of depression. The first paper reviews many of the physiological abnormalities found in depression and the reversal or normalization of these same systems by meditation. The paper includes 1) a review of the physiological concomitants of depression, 2) a description of mindfulness meditation and its effects on mood disturbance, 3) the physiological effects of mindfulness and other related forms of meditation, and 4) suggestions for future research.

The second paper summarizes the results of a randomized controlled trial of mindfulness meditation training on one of the previously identified candidate systems: sleep, as measured by overnight polysomnographic sleep studies as well as subjective reports (sleep diaries). The results indicate that mindfulness has an arousing effect on objectively measured sleep that corresponds with subjectively reported improvements in mood and sleep. This pattern is similar to the one observed in responders to antidepressant medications.

INTRODUCTION

This dissertation represents a three-year research endeavor that investigated the possible physiological mechanisms of mindfulness meditation's therapeutic effects in depression. The first step in the process was to review the pathophysiology of depression, including changes in the brain, endocrine, immune and neurotransmitter systems. The second step was to review the available literature on the physiological effects of meditation, primarily mindfulness meditation, but also other types, in order to determine if the systems affected by meditation overlapped with those disturbed in depression. The third step was to identify the candidate systems that met the following criteria: a) involvement in the pathophysiology of depression b) a tendency to remain disturbed after clinical remission and therefore increase likelihood of relapse, c) evidence that the system is affected or normalized by mindfulness or other forms of meditation. The fourth step was to develop a research project that could investigate the effects of mindfulness meditation on several of the identified candidate systems in partially remitted depression sample, based on available funding, space, personnel, expertise and time constraints. The fifth and final step was to conduct the research and write up the results.

The first four steps, the literature reviews and the development of the model, are represented by an introductory review paper entitled "Reversal of depression-related physiology by meditation: a prelude to possible mechanisms of action" which can be found in Appendix A. The paper was co-authored by Richard Bootzin, Jessica Payne, John Allen and Francisco Moreno. Dr. Bootzin contributed to the sections on sleep, Dr. Allen contributed to the sections on frontal asymmetry and vagal tone, Dr. Payne

contributed to the sections on stress and memory, and Dr. Moreno contributed to the sections on psychopharmacology, neurotransmitter systems, depression subtypes and course of illness.

The research project included the investigation of mindfulness meditation on several candidate systems, including a) functioning of areas known to be disturbed in depression (hippocampus, amygdala, prefrontal cortex, anterior cingulate), b) endocrine functioning (cortisol reactivity), c) sleep d) neurotransmitter systems (catecholamines), f) vagal tone g) and frontal EEG asymmetry. The results of the investigation of one candidate system, sleep, is reported here in a paper entitled "Effects of mindfulness meditation on electroencephalographic sleep profiles" that can be found in Appendix B, and also summarized in the following section. The paper was co-authored by Patricia Haynes, Keith Fridel and Richard Bootzin. Dr. Haynes co-supervised the statistical analysis and contributed to issues of empirical validity. Dr. Fridel is a registered polysomnographic sleep techinician (RSPSGT), scored all of the sleep records and contributed to sections on polysomnographic and sleep parameters. Dr. Bootzin co-supervised the statistical analysis and contributed to the paper as a whole.

PRESENT STUDY

The methods, results and conclusions of this study are presented in the paper appended to this dissertation. The following is a summary of the most important findings in this document.

Contrary to previous research and predictions that mindfulness meditation would improve or deepen sleep, several findings from this study suggest that mindfulness has an arousing effect on objectively measured sleep. First, individuals randomly assigned to an 8-week mindfulness meditation program exhibited a suppression of slow-wave sleep compared to waitlisted controls. Second, antidepressant medication-free individuals in the mindfulness group showed a significant increase in awakenings, arousals and stage 1 sleep from pre- to post-treatment. Third, there was a significant negative correlation between the amount of meditation practice and the need for sleep, such that the more minutes of meditation per week, the less time spent in bed or sleeping.

APPENDIX A: REVERSAL OF DEPRESSION-RELATED PHYSIOLOGY BY MEDITATION: A PRELUDE TO POSSIBLE MECHANISMS OF ACTION

Running Head: Meditation and Depression

Reversal of depression-related physiology by meditation: a prelude to possible mechanisms of action

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Abstract

Although meditation-based interventions have been associated with improvement in depressive symptoms and prevention of relapse, the physiological mechanisms of meditation's therapeutic effects are unknown. At the same time, a growing body of literature has shown that meditation has profound effects on numerous physiological systems that are involved in the pathophysiology of depression. This paper reviews many of the physiological abnormalities found in depression and the reversal or normalization of these same systems by meditation. The paper includes 1) a review of the physiological concomitants of depression, 2) a description of mindfulness meditation and its effects on mood disturbance, 3) the physiological effects of mindfulness and other related forms of meditation, and 4) suggestions for future research.

Keywords: depression, meditation, physiology, stress, mindfulness

Introduction

Major depression is a debilitating mood disorder that affects almost 19 million adults in the U.S at any given time (Narrow, 1998) and almost 20% of the U.S. population over a lifetime (Blazer, Kessler, McGonagle, & Swartz, 1994). In the year 2020, depression is predicted to be the largest cause of disease burden in women and the second largest cause of disability adjusted life years worldwide, second only to ischemic heart disease (Murray & Lopez, 1996). In the U.S., the economic burden of depression has gone up from $43.7 billion in 1990 (Greenberg, Stiglin, & Finkelstein, 1993) to almost $53 billion in 2000 (Greenberg et al., 2003). Indirect consequences of depression are troublesome as well, and include increased failure to finish high school (Kessler, Foster, & Saunders, 1995) likelihood of divorce (Kessler, Foster, & Saunders, 1998), and substance abuse (Abraham & Fava, 1999).

It should be noted that Major Depressive Disorder (MDD) is not a discrete condition but rather a cluster of signs and symptoms that include depressed mood, and or lack of interest or pleasure, and at least fours symptoms from a list that includes: weight or appetite changes; sleep changes; observable changes in psychomotor activity; feelings of worthlessness or guilt; poor ability to think or concentrate, or make decisions; and recurrent thoughts of death or suicide (APA 2000). Separate unipolar depressive syndromes have been conceptualized as “research categories” in DSM-IV-TR (minor depressive disorder, recurrent brief depressive disorder, and premenstrual dysphoric disorder), and patients with MDD may be further subdivided by a variable clinical status (severity, chronicity, recurrence), and may possess specific clinical features such as

"psychotic, melancholic, atypical, catatonic, or postpartum onset". The high heterogeneity in depressive disorders represents a significant challenge to the biological and treatment studies of MDD. While it is believed that certain subtypes of depression may have a distinctive course, long-term prognosis, treatment response, and neurobiology, many studies have failed to classify their participants into clinical subcategories. Therefore, subtype information may not be available for each section of the following review of neurobiological concomitants of depression.

While antidepressant medication is the most popular treatment for depression, large meta-analytic studies report an intent-to-treat analysis response rate of approximately 55% and about 70% for study completers (Fava & Davidson, 1996). Furthermore, patients who meet response criteria may remain partly symptomatic, disabled, and at higher risk of relapse (Nierenberg, Keefe, & Leslie, 1999). When the more stringent outcome criteria is utilized, remission rates reportedly vary from 35 to 45% (Thase, 2003; Thase, Entsuah, & Rudolph, 2001).

Pharmacological treatments can be expensive, may often be accompanied by nuisance side effects, and at times safety concerns. Limitations in access to care, compliance, and efficacy affect our ability to adequately treat depression, and highlight the need for novel treatment techniques. Meanwhile, the use of complementary and alternative medicine (CAM) therapies for depression is on the rise. A recent national survey indicated that more than half of respondents (54%) with self-diagnosed depression indicated that they used some form of CAM therapy for their depression, while only 36% reported that they consulted a physician or other mental health professional for

depression (Kessler et al., 2001). The increased public interest and use of CAM therapies and the simultaneous rise in criticism of current treatments demands detailed explorations of these rising therapies. This paper will focus on one particularly promising CAM intervention that, in its early stages of research, has been found to be helpful in improving depressive symptoms and preventing relapse – mindfulness and other forms of meditation.

In spite of its wide use for emotional disturbance, the mechanisms underlying the effectiveness of mindfulness-based treatments are poorly understood. To date, the vast majority of proposed mechanisms have been cognitive. Yet mindfulness and other related forms of meditation have profound effects on numerous physiological systems, many of which are believed to play a role in the pathophysiology of depression.

This paper integrates research findings from two areas that have previously remained distinct: the physiology of depression and the physiological effects of meditation. The review of depression physiology focuses on the most consistent physiological abnormalities found in depression, with specific attention to systems that have been found to be affected by meditation. This section is intended to provide a broad audience with an overview of the various interrelated systems implicated in the pathophysiology of depression so that the effects on these systems by meditation may be understood in the context of therapeutic significance. Similarly, the review of the physiological effects of meditation is limited to physiological systems implicated in depression, and by the type of meditation, with a focus on the two largest research literatures: Mindfulness and to a lesser extent, Transcendental Meditation (TM).

As the reviews will demonstrate, the physiological changes associated with meditation practice appear to reverse or counteract those seen in depression. The normalization of these systems may begin to comprise a model to explain the underlying mechanism of action of mindfulness interventions for depression. The paper includes 1) a review of the physiological concomitants of depression, focusing especially on the disruption of stress systems, 2) a description of mindfulness meditation, 2) meditation effects on mood disturbance, 3) the physiological effects of mindfulness and other related forms of meditation, and 4) suggestions for future research.

The Neurophysiological Concomitants of Depression

As will be seen, the pathophysiology of depression is similar to that seen in models of chronic stress, and the link between stress and depression is well-known. Early episodes tend to be triggered by stressful life events (Mazure, 1998) and the biological changes resemble a multi-system stress reaction. However, later episodes of depression tend to become less dependent on external stressors, as the underlying stress systems become more endogenously activated, a phenomenon referred to as “kindling” (Hammen, 2005; Kendler, Thornton, & Gardner, 2000; Monroe & Harkness, 2005; Post, 1992; Post, Rubinow, & Ballenger, 1984).

Stress and its biochemical consequences have profound and differential effects on brain areas related to cognitive and emotional regulation, immune function, neuroendocrine and neurotransmitter activity, and sleep, all of which are believed to be involved in the pathophysiology of depression. As the accelerating course of depression suggests, the biology changes as the illness progresses, and as compensatory systems

become more impaired. It should also be noted that the story is not clear-cut and that considerable uncertainty still remains as to whether many of the biological disturbances observed in depression are precursors, state or trait markers, or residual scars of the illness.

Neurotransmitter Theories of Depression:

One of the earliest physiological models of depression posits that depression results from reduced availability of monoamine neurotransmitters, particularly serotonin (5-HT) and norepinephrine (NE) and to a lesser extent, dopamine (DA) (Coppen, 1967; Schildkaut, 1965). This theory emerged from observations that monoamine depleters (reserpine) could induce depression and that monoamine enhancers had antidepressant effects. Subsequent findings, however, challenged this model. For example, catecholamine and 5-HT depletions are likely to induce depressive symptoms in remitted depressive subjects and healthy volunteers with family history of mood disorders. However, individuals without personal or family history of affective disorders are unlikely to experience depressive responses during these depletions (Delgado & Moreno, 2000). In addition, some antidepressant medications actually *decrease* extracellular levels of monoamines by enhancing reuptake (Ansseau, 1993). And finally, antidepressant drugs cause immediate increases in synaptic monoamines, but symptom improvement is typically delayed by about three weeks, or may not be present at all (Sulser, Vetulani, & Mobley, 1978).

As a result, the "receptor sensitivity hypothesis" of antidepressant action was proposed. This hypothesis stated that the delayed therapeutic effects of antidepressant

treatment were related to time-dependent alterations in catecholeamine and indoleamine receptor sensitivity, and implied that the pathophysiology of depression may be more related to abnormal regulation of receptor sensitivity than to deficiencies of a neurotransmitter (Charney, Menkes, & Heninger, 1981). The "dysregulation hypothesis" was subsequently expressed by Siever and Davis (1985). The dysregulation hypothesis proposed that in affective disorders, regulatory or homeostatic mechanisms controlling neurotransmitter function were dysregulated, and that effective pharmacologic agents would restore normal regulation to these systems (Siever & Davis, 1985). The dysregulation and receptor sensitivity hypotheses went beyond neurotransmitter deficiencies, proposing that functional deficits in neurotransmission could occur with normal monoamine neurotransmitter content.

Although monoamine theories of depression continue among the most popular biological hypotheses for depression, it remains unclear whether the dysfunction of 5-HT and NE may be related to neurotransmitter availability (Coppen, 1967; Martensson, Nyberg, Toresson, Brodin, & Bertilsson, 1989; Mendels, Frazer, Fitzgerald, Ramey, & Strokes, 1972; Schildkaut, 1965), receptor responsivity (Charney et al., 1981), or intracellular mechanisms potentially responsive to these or other molecules (Duman et al., 1997). Thus, alternative models have been proposed. Disturbances in other neurotransmitter systems, including GABA (Petty, 1995), glutamate (Auer et al., 2000; Kim, Schmid-Burgk, Claus, & Kornhuber, 1982), acetylcholine (Fritze, 1993; Leboyer & Plaisant, 1985) and nitric oxide (NO), a non-traditional multifunctional vascular, immune and neural signaling molecule have also been proposed as vulnerability hypotheses for

depression (Chrapko et al., 2004; Esch, Stefano, Fricchione, & Benson, 2002; Selley, 2004). In addition, other neurohormones and peptides are thought to mediate aspects of stress response and mood regulation. These include among others: thyrotropin releasing hormone, thyrotropin, growth hormone releasing hormone, growth hormone, somatostatin, vasopressin, oxytocin, allopregnanolone, neurotensin, neuropeptide-Y, and substance P. Discussions on the role of these peptides is beyond the scope of this paper, and are available elsewhere (Nemeroff, 1991). It is possible that many of these signaling molecules that are dysregulated in depression may be linked to a shared pathway related to stress, neurogenesis and synaptic plasticity (Duman, Heninger, & Nestler, 1997; Duman, Malberg, Nakagawa, & D'Sa, 2000).

Stress and the HPA Axis

Many of the neurophysiological abnormalities that are often found in depression are consistent with those found in chronic stress or chronic sympathetic nervous system hyperactivation with a concomitant hypoactivation of the parasympathetic system. One of the most consistent biological findings in depression is the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, a part of the sympathetic stress response system that consists of a circuit between the hypothalamus, pituitary and adrenal glands. Although the stress response system is complex, with many mediators and feedback loops, the most basic stress response begins with release of corticotropin-releasing factor (CRF) from the hypothalamus. CRF stimulates the anterior pituitary to release adrenocorticotropin hormone (ACTH) into the blood and ACTH stimulates the adrenal cortex to release glucocorticoids such as cortisol.

In about 20-40% of depressed outpatients and 60-80% of depressed inpatients, the HPA axis shows signs of hyperactivation and disinhibition as evidenced by enlarged pituitary and adrenal glands, increased levels of CRF and increased levels of cortisol (Carroll, Curtis, & Mendels, 1976). While hypercortisolemia may be present in other mental disorders (such as schizophrenia, and PTSD), its likelihood increases with the intensity of dysphoric arousal regardless of disorder (Thase & Howland, 1995). For reviews see Claes, (2004), or Thase, Jindal, & Howland (2002).

The HPA axis contains at least two negative feedback loops that serve to prevent hyperactivation. First, circulating endogenous glucocorticoids (like cortisol) feed back to the hypothalamus and pituitary to inhibit secretion of CRF and ACTH. Second, the hippocampus and parts of the frontal cortex also aid in negative feedback to the pituitary and hypothalamus. Because the hippocampus is involved in negative feedback control of cortisol (Jacobson & Sapolsky, 1991), disruption and atrophy of the hippocampus (for example, via glucocorticoids, cytokines, glial loss, trophic factor deficits) may result in the hypercortisolemia seen in some subjects with depression (Goodyer et al., 1996); or the lack of suppressor response to dexamethasone administration also observed in subsets of depressive subjects (Goodyer et al., 1996).

HPA axis activation and stress are also intricately connected with NE and 5-HT activity (Linthorst, Flachskamm, Holsboer, & Reul, 1994), two neurotransmitters believed to be dysregulated in depression and the most common targets of pharmacological treatments. While increased stress-induced HPA activity increases both 5-HT and NE activity, 5-HT exerts inhibitory feedback, and NE tends to stimulate CRH

release (Barden, 2003; Pacak, Palkovits, Kopin, & Goldstein, 1995). Thus, disruption in these monoamine systems can have profound effects on the HPA axis and vice versa, although it remains unclear if any of these systems mediate depression.

Immune disturbances:

Immune changes are a common physiological concomitant of stress and depression. Studies of immune changes in depression have often yielded what appear to be inconsistent results, suggesting both activation and suppression of the immune system in depression. However, the immune system collectively has as many cells as the brain or liver and these cells have diverse functions that may not be correlated with each other. In brief, an immune response can be broken down into two phases: an initial, global or non-specific response, and a secondary specific response. The non-specific response, also called the acute phase proinflammatory response is a reaction most commonly triggered by infection that is mediated by leukocytes. When activated by foreign antigens, leukocytes synthesize and release singnaling molecules called proinflammatory cytokines or interleukins that attract other types of immune cells to the affected site and start a cascade of events throughout the body known as the acute phase response. Some of the cytokines important to the acute phase response are interleukin-6 (IL-6), interleukin-1 (IL-1), interferon-gamma (IFNγ) and tumor necrosis factor-alpha (TFNα).

The specific immune response is mediated through lymphocytes like cytotoxic T-cells, helper T-cells, B-cells and natural killer cells (NK). When activated by the right cytokine, helper T-cells can be stimulated to proliferate and to activate B-cells that in turn

make antibodies specifically against the foreign antigen. Once antibodies bind to the foreign antigen, they activate processes that destroy the antigen.

In depression, although there is much variability, immune changes often mirror those seen in chronic stress, with an elevation of the first phase (non-specific response) and a suppression of the second (specific immunity). For example, the (non-specific) acute phase pro-inflammatory response system, is activated by both physical and psychological stressors (Marazziti, Di Muro, & Castrogiovanni, 1992; Renbourn, 1960; Shintani et al., 1995; Zhou, Kusnekov, Shurin, De Paoli, & Rabin, 1993), and often shows signs of hyperactivity in depression. Specifically, acute phase pro-inflammatory cytokines interleukin-1-beta (IL-1β), interleukin-6 (IL-6) and interferon-gamma (IFNγ) are immune compounds that are commonly elevated in depression (Irwin, 1999). At the same time, specific immunity, is usually suppressed by stress (Glaser et al., 1993) and negative mood (Futterman, Kemeny, Shapiro, & Fahey, 1994; Knapp et al., 1992), and tends to be suppressed in depression, as evidenced by reduced lymphocyte (T-cells, B-cells) and natural killer (NK) activity (Irwin, 1999).

While it is believed that depression causes immune changes, empirical evidence suggests that the opposite may also be true, so that immune changes may precede depressive symptoms, perhaps as a consequence of a prolonged stress response, and it may play a role in the mechanism for development of depressive symptoms. A number of studies in both animals and humans have demonstrated depressogenic effects of immune compounds. For example, peripheral administration of the immune stimulating compound lipopolysaccaride (LPS; also called “endotoxin”), or the proinflammatory

cytokines IL-1 and IL-6 induce a depression-like syndrome in animals characterized by anorexia, weight loss, anhedonia, sleep disorders, and suppression of social, locomotor and exploratory behavior (Anisman, Kokkinidis, Borowski, & Merali, 1998; Dantzer et al., 1998; Linthorst & Reul, 1998; Maier & Watkins, 1995, , 1998). For example, rats who have received LPS no longer show a preference for a sucrose solution over water (Yirmiya, 1996). Similarly, administration of cytokines IL-2 and IFNγ often induce major depressive episodes in humans (McDonald, Mann, & Thomas, 1987).

Further supporting the role of the immune system in depression, reversal of these immune changes often coincide with the amelioration of depressive symptoms. In fact, most antidepressants, including SSRIs, tricyclics and heterocyclic antidepressants have been found to have anti-inflammatory effects (Xia, Depierre, & Nassberger, 1996). Antidepressants may exert their anti-inflammatory effects by inhibiting proinflammatory cytokines or by upregulating anti-inflammatory compounds called "negative" or "immunoregulatory" cytokines that block or reverse immune system activation. IL-10, IL-4 and an IL-1 receptor antagonist (IL-1ra) are examples of negative immunoregulatory cytokines. The antidepressants clomipramine, desipramine, sertraline and trazadone have been shown to suppress production of IFNγ and stimulate the production of IL-10 and IL-1ra (Kubera et al., 1998; Maes et al., 1999; Suzuki, Shintani, Kanba, Asai, & Nakaki, 1996). Other studies have found no relationship between cytokines and depression levels, especially in less severe cases (Irwin, Clark, Kennedy, Christian Gillin, & Ziegler, 2003).

Vagal tone

Depression has often but not universally been characterized by hypoactivation of the parasympathetic nervous system, as manifested by changes in cardiac variability. Vagal tone, or respiratory sinus arrythmia (RSA), refers to heart rate variability (HRV) that occurs at the frequency of breathing (.12-.4 Hz) and is considered an index of parasympathetic activity (Grossman, Stemmler, & Meinhardt, 1990). A number of studies suggest that depressed individuals have a lower vagal tone than non-depressed controls (Dalack & Roose, 1990; Rechlin, Weis, & Kaschka, 1995; Rechlin, Weis, Spitzer, & Kaschka, 1994; Roose, Glassman, & Dalack, 1989), although not all studies have substantiated this finding (Moser et al., 1998; Rechlin, 1994). Lower vagal tone has been found to be associated with negative emotions (Calkins, 1997; Cole, Zahn-Waxler, Fox, Usher, & Welsh, 1996), particularly sadness (Rechlin et al., 1995), and higher vagal tone has been shown to predict greater self-reported regulatory control and decreased negative emotional arousal in the face of moderate-to-high level stressors (Fabes & Eisenberg, 1997). Furthermore, increases in vagal tone and the related construct of HRV have been found to parallel positive response to both pharmacological (Balogh, Fitzpatrick, Hendricks, & Paige, 1993; Khaykin et al., 1998) and non-pharmacological (Carney et al., 2000; Chambers & Allen, 2002) treatments.

Sleep

Sleep abnormalities in depressed individuals parallel those of stressed individuals, showing multiple signs of hyperarousal, as indicated by increased sympathetic (rapid eye movement sleep or REM) influence over parasympathetic slow-wave (non-rapid eye

movement or NREM sleep stages 3-4) activity, particularly during the early REM/NREM cycles of the sleep period (Hall et al., 2004). Depression-related sleep abnormalities have been grouped into three categories: sleep continuity disturbances, slow-wave sleep (SWS) deficits, and REM sleep abnormalities (Reynolds & Kupfer, 1987). For reviews of sleep and depression, see Benca (2000), Benca, Obermeyer, Thisted, and Gillin (1992), Reimann, Berger, and Vodenholzer (2001), and Reynolds and Kupfer (1987). Sleep continuity disturbances which are among the diagnostic criteria for depression, include reports of sleep onset insomnia, sleep maintenance problems, and early morning awakenings. There has been increasing evidence that sleep disturbances are not only concomitant symptoms of depression, but are also risk factors for both new and recurrent episodes of depression (Breslau, Roth, Rosenthal, & Andreski, 1996; Perlis, Giles, Buysse, Tu, & Kupfer, 1997).

REM sleep abnormalities in depression show signs of disinhibition, as manifested by early onset REM sleep (Kupfer, 1976), increased REM sleep duration in the first cycle (Benca et al., 1992), and increased REM density (Vogel, Roth, Gillin, Mendelson, & Buffenstein, 1988). The increased prevalence or "density" of rapid eye movements during REM sleep in depressed individuals has received a growing amount of attention. Increased REM density, either in the first REM sleep period or averaged across all REM sleep periods, is one of the most reliable findings in depression (Gillin et al., 1981; Lauer, Riemann, Wiegand, & Berger, 1991; Riemann et al., 2001; Wichniak, Riemann, Kiemen, Voderholzer, & Jernajczyk, 2000).

Supporting the hypothesis that uninhibited REM sleep is a pathophysiological mechanism in depression, most antidepressant medications, including tricyclics, MAOIs and SSRIs, produce large sustained reductions in REM sleep (Riemann et al., 2001). In addition, nonpharmacological REM sleep deprivation has been found to exert an antidepressant effect with the same delayed time-course as antidepressant medications (Vogel, Vogel, McAbee, & Thurmond, 1980). Imaging studies of REM sleep vs. wake in depressed individuals vs. non-depressed controls showed increased activation in limbic and paralimbic affect-related structures like the amygdala, hippocampus and anterior cingulate in depressed individuals, which may reflect the affect dysregulation seen in depression (Nofzinger, Buysse, Germain, Carter et al., 2004). In addition, depressed patients showed greater activation during REM sleep of cortical regions associated with executive functioning (Nofzinger, Buysse, Germain, Carter et al., 2004). This may reflect the cognitive dysfunction experienced by depressed patients. Consequently, sleep disturbances of depressed patients may provide a means of identifying brain mechanisms related to the nature and severity of their emotional and cognitive dysregulation.

In contrast to REM sleep, which shows signs of disinhibition, slow-wave sleep (NREM stages 3 and 4) is often reduced in depression (Lauer et al., 1991; Reynolds & Kupfer, 1987). Data from electroencephalographic (EEG) studies of depressed individuals indicate increased fast and/or decreased slow frequency EEG activity (Kupfer, Frank, McEachran, & Grochocinski, 1990; Nofzinger et al., 2000) in early NREM sleep that is associated with both behavioral arousal (Merica, Blois, & Gaillard, 1998) and increased cortisol/HPA activity (Chapotot, Gronfier, Jouny, Muzet, &

Brandenberger, 1998), and negatively correlated with self-reported sleep quality (Nofzinger et al., 2000). Imaging studies indicate that the usual deactivation of the prefrontal cortex at sleep onset, which has been called a potential "defining characteristic of sleep itself" (Braun et al., 1997), is reduced in depressed individuals (Germain, Nofzinger, Kupfer, & Buysse, 2004). This abnormal level of activation during sleep may be associated with the sleep discontinuity and non-restorative sleep commonly found in depression and insomnia (Nofzinger, Buysse, Germain, Price et al., 2004).

A number of theories have been proposed to integrate the sleep and depression findings. Prominent among them are theories that depressed individuals are hyperaroused and have a deficiency in parasympathetic SWS-generating mechanisms controlled by a homeostatic process S and/or a hyperactivation of sympathetic REM sleep mechanisms controlled by a circadian process C (Borbely & Wirz-Justice, 1982). Since neurotransmitters associated with SWS (monoamines) and REM sleep (acetylcholine) reciprocally inhibit each other (Hobson & McCarley, 1975), deficiency in one can appear as overactivity in the other and vice versa. In line with this view, deficits in monoamines (5-HT and NE, which usually inhibit REM sleep) may be linked to REM sleep disinhibition in depression. Or alternatively, an excess in acetylcholine (which facilitates the onset and duration of REM sleep) may be responsible for REM disinhibition. Imaging studies of REM sleep vs. wake in depressed individuals vs. non-depressed controls have shown hyperactivation of limbic (amygdala) and brain stem structures that are densely innervated with both acetylcholine and CRH, which supports a cholinergic/monoaminergic imbalance theory as well as a hyperactive stress system

theory (Nofzinger, Buysse, Germain, Carter et al., 2004; Thase et al., 2002). There is accumulating evidence that increases in CRH can account for many of the stress and depression related abnormailities, including increased, REM sleep, wake and high frequency EEG, and decreases in low frequency bands and slow-wave sleep (Opp, 1995). Similarly, direct stimulation of the amygdala, which is activated by CRH and cortisol, induces REM sleep in animals (Smith & Miskiman, 1975).

This combination of REM sleep disinhibition and decreased sleep maintenance identifies about 40% of depressed outpatients and 80% of depressed inpatients, but only about 10% of age-matched healthy controls, and therefore is a sensitive indicator (Thase et al., 1997). However, these sleep abnormalities have also been reported in other psychiatric disorders (including panic disorder, post-traumatic stress disorder, alcoholism, borderline personality disorder, schizophrenia, and schizoaffective disorder) (Benca et al., 1992; Benca, 2000). Partially this reflects the presence of comorbid mood disorders in other disorders. However, it may also be the case that similarities in sleep abnormalities may indicate a similar pathophysiology (Benca, 2000).

Neurotoxic effects of stress

Elevated levels of the stress hormone cortisol, like those seen in depression, can have neurotoxic effects on brain areas that are high in glucocorticoid receptors, such as the hippocampus and prefrontal cortex (PFC). Stress/cortisol's deletrious effects on neurons ranges from synapse loss (Magarinos & McEwen, 1995) and disruption of plasticity (Filipini, Gijsbers, Birmingham, & Dubrovsky, 1991), to decreased neuronal growth/neurogenesis (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998) and, perhaps,

even neuronal death (Uno, Ross, Else, Suleman, & Sapolsky, 1989). Chronic depression and other syndromes that are characterized by high levels of glucocorticoids are associated with hippocampal volume loss that is proportionate to the duration of illness, independent of age (Sheline, Sanghavi, Mintun, & Gado, 1999). Loss of hippocampal neurons and decreased glucose metabolism in the hippocampi of patients with depression has been found in numerous magnetic resonance imaging (MRI) and positron emission tomography (PET) studies (Bremner et al., 2002; Mervaala et al., 2000; Sheline et al., 1999; Sheline, Wang, Gado, Csernansky, & Vannier, 1996; Steffens et al., 2000).

In addition to hippocampal damage, high levels of cortisol also affect the PFC. The medial portion of the PFC exerts a tonic inhibitory influence on the amygdala, and therefore disruption of the PFC disinhibits the amygdala (Rosenkranz & Grace, 2002). Thus, high levels of stress and glucocorticoids may cause hyperactivation of the amygdala by disrupting the PFC. Reduction of amygdalar hyperactivation by antidepressants parallels depressive symptom improvement, (Davidson, Pizzagalli, Nitschke, & Putnam, 2002), which supports the idea that this stress-induced disinhibition of the amygdala may be a key neurophysiological concomitant of depression.

While stress's deleterious effects on the hippocampus have traditionally been thought to be mediated entirely by glucocorticoids, there is increasing evidence that acute phase proinflammatory response protein interleukin-1 (IL-1) which is released by macrophages in response to stress, may also contribute to stress-related hippocampal dysfunction (Aubert, Vega, Dantzer, & Goodall, 1995; Gibertini, Newton, Friedman, & Klein, 1995; Linthorst et al., 1994).

Stress, Neurogenesis and Depression

Depression has been linked not only to the neurotoxic effects of stress-related substances like cortisol and IL-1, but also to a disruption of neurogenesis and synaptogenesis, or the growth of new neurons and synapses. Neurogenesis, which occurs largely in the hippocampal region of the brain, may be hampered by the overactivation of the stress system, and/or by the dysregulation of a number of substances with neurotrophic properties, such as estrogen, 5-HT and brain-derived neurotrophic factor (BDNF).

The idea that depression and neurogenesis are linked comes from several lines of evidence. First, stress, which suppresses neurogenesis, can also trigger bouts of depression (Lloyd, 1980; Mazure, 1998). Stress can cause cell death (Uno et al., 1989), dendritric shrinkage (Magarinos & McEwen, 1995) and markedly reduced levels of neurotrophins within the hippocampus (Smith, Makino, & Kvetnansky, 1995), as well as cause an impairment in hippocampal granule cell neurogenesis (Gould et al., 1998). Individuals with depression exhibit signs of neural loss in the same areas as individuals with other stress-related syndromes (Sheline et al., 1999). For example, post mortem and brain imaging studies have revealed atrophy or loss of neurons in the prefrontal cortex and hippocampus of both depressed and anxious patients (Bremner et al., 2002; Mervaala et al., 2000; Sheline et al., 1999; Sheline et al., 1996; Steffens et al., 2000). Third, medications that improve depressive symptoms also promote neurogenesis in the hippocampus, and reverse depression-related atrophy (Castren, 2004; Siuciak, Lewis, Wiegand, Stanley, & Lindsay, 1997). It is still unclear whether these alterations

contribute significantly to clinical depression. However, the fact that adult hippocampal neurogenesis is impaired by stress and facilitated by antidepressant treatment suggests that neurogenesis may play a critical role in the pathogenesis of depression.

The link between stress, neurogenesis and depression is illustrated by the common effects of stress on three trophic factors which usually aid the growth of neurons: estrogen, 5-HT and BDNF. All three are suppressed by stress, which results in both reduced neurogenesis and depression. Thwarted neurogenesis and depressive symptoms are concurrently ameliorated when these trophic factors are increased, and each trophic factor is independently a strong antidepressant. Each trophic factor and its role in depression will be discussed below.

As described above, estrogen is a powerful neurotrophic factor (Tanapat, Hastings, Reeves, & Gould, 1999) that is associated with dendritic branching and synapse formation in the hypothalamus and hippocampus during the first days of the menstrual cycle and dendritic pruning as estrogen levels fall (Foy, 2001; Li et al., 2004; Scharfman, Mercurio, Goodman, Wilson, & MacLusky, 2003). Fluctuations in estrogen associated with down-regulation of dendritic spine formation correlate with premenstrual dysphoric disorder and menopause, suggesting a link between decreased neurogenesis and depressive symptoms (Genazzani, Monteleone, & Gambacciani, 2002). Conversely, estrogen has been known to exert powerful antidepressant effects and augment pharmacological therapy (Panay & Studd, 1998; Price & Giannini, 1985) . Stress exposure and glucocorticoid elevations profoundly reduce estrogen levels (Sapolsky,

2001), which may be yet another pathway by which stress decreases neural growth in the hippocampus.

Serotonin, while traditionally thought of as a neurotransmitter, is also a powerful trophic factor that is involved in regulating both synaptogenesis and neurogenesis. As a neurotransmitter, 5-HT produces rapid post-synaptic alterations. As a trophic factor, it can effect the functioning of target cells by causing the release of glial-derived trophic factors. Activation of 5-HT receptors, especially the 5HT1a subtype, in the hippocampus enhances neurogenesis, stimulates the growth of new cells and synapses (Jacobs, Tanapat, Reeves, & Gould, 1998), while lesions of the serotonin system decrease neurogenesis (Brezun & Daszuta, 2000) and result in loss of synapses (Cheng, Hamsguchi, Ogawa, Hamada, & Okada, 1994; Wilson, Faber, & Haring, 1998), loss of synaptic proteins (Azmitia, Rubinstein, Strafaci, Rios, & Whitaker-Azmitia, 1995) and decreased levels of glial-derived trophic factors (Haring, Hagan, Olson, & Rodgers, 1993). Many serotonergic agents both reverse cell loss and synaptic pruning while also ameliorating depressive symptoms, which supports the idea that depression may be related to impaired neurogenesis (Lista Varela, 2003).

Because of its role as a trophic factor and its sensitivity to stress, the 5-HT system may mediate stress-related synapse loss that is implicated in depression. For example, several studies have demonstrated that cortisol secretion triggered by repeated stress reduces expression of the gene that codes for the 5-HT1a receptor. This 5-HT receptor is profoundly reduced, in some cases by nearly a third (Neumeister et al., 2004), in key brain regions of patients with panic disorder and co-morbid depression,

particularly those regions that are important for regulating 5-HT production and mood (Drevets et al., 1999).

In addition to reducing trophic factors like 5-HT and estrogen, stress and glucocorticoid release lead to a dramatic decrease in BDNF (Smith, Makino et al., 1995) that results in hippocampal atrophy. These stress-induced changes in neurogenesis and neuroplasticity can be reversed by direct BDNF administration (Siuciak et al., 1997) and by antidepressant therapy (Castren, 2004; Malberg, 2004), including monoamine enhancers (Nibuya, Morinobu, & Duman, 1996) and electroconvulsive therapy (ECT) (Krystal & Weiner, 1999) which all increase BDNF levels and improve symptoms. BDNF, like estrogen and 5-HT, increases neurogenesis and exerts antidepressant effects (Siuciak et al., 1997), which strengthens the link between neural growth and depression.

In addition to disrupting trophic factors, stress may interrupt the neurogenic climate and induce depression by increasing pro-inflammtory cytokines. As described above, cytokines are released in response to stress, are elevated in depression and can induce depressive symptoms in both humans and animals. A recent study also showed that elevated pro-inflammatory cytokines disrupt the birth of new neurons in the hippocampus and blockade of inflammation with the non-steroidal anti-inflamatory drug indomethacin restored neurogenesis (Monje, Toda, & Palmer, 2003). Antidepressant medications also tend to have anti-inflammatory effects, which together suggests the link between cytokines, the health of the neurogenic environment and depression.

Some of the best evidence to date that changes in neurogenesis might at least partly underlie depression comes from a study by Santarelli et al., (2003), who

investigated whether an increase in neurogenesis is *required* for the behavioral effects of antidepressants in an animal model of depression. After 1 month of antidepressant treatment, mice showed a significant improvement in depression and anxiety symptoms (e.g. willingness to eat in a brightly lit, unfamiliar environment). As in previous studies, this improvement was associated with a substantial (in this case, 60%) increase in the number of dividing cells in the hippocampus. Their critical finding, however, was that blocking neurogenesis with radiation also blocked the therapeutic effects of antidepressants. The irradiated mice failed to produce new neurons and they were completely unresponsive to the typical behavioral benefit of the antidepressant treatment. These experiments are some of the first to suggest a cause-and-effect relationship between the growth of new neurons in the hippocampus and depression, at least in an animal model. Given that the neurogenesis process takes time – stem cells must divide, differentiate, migrate and establish appropriate connections, a process that takes a few weeks - it is possible that the month-long delay in antidepressant effectiveness is related to neurogenesis.

Thus, a multitude of physiological systems that are involved in the mediation of neuronal growth and plasticity are implicated in depression, and are strongly influenced by stress (see Table 1 for summary). To review, stress-related compounds like glucocorticoids and proinflammatory cytokines, which are elevated in depression, impair the growth of new neurons and synapses, particularly in the hippocampus and prefrontal cortex. Substances that promote neuronal growth, such as estrogen, 5-HT and BDNF are reduced in depression, and their restoration to normal levels improves depressive

symptoms. Furthermore, disruption of the antidepressant-induced neurogenesis blocks the behavioral effects of these medications, suggesting that neurogenesis may be one of the mechanisms behind their efficacy (Santarelli et al., 2003). Altogether, these findings suggest that thwarted neurogenesis and neuroplasticity may be a central underlying mechanism of depressive pathophysiology, an idea that has been proposed and supported by many researchers (D'Sa & Duman, 2002; Duman, 2004; Gould, Tanapat, Rydel, & Hastings, 2000; Lee, Ogle, & Sapolsky, 2002; Malberg, 2004; Sapolsky, 2000; Sheline, 2000).

insert Table 1 about here

Functional Neuroanatomical Abnormalities

A number of brain abnormalities are consistently found in depression, many of which parallel those found in chronic stress. These include hypoactivation of areas of the prefrontal cortex, the anterior cingulate cortex, and the hippocampus and hyperactivation of the amygdala. (For a review, see Davidson, Pizzagalli, Nitschke, & Putnam (2002) or Drevets (2001)).

Neuroimaging studies of depressed patients have yielded a pattern of reduced resting cerebral blood flow (CBF) or metabolism in the PFC and the anterior cingulate cortex (ACC) in comparison to age and gender-matched never-depressed individuals. Prefrontal hypoactivation consistently includes dorsolateral and dorsomedial regions, particularly on the left side (Baxter et al., 1989; Bench, Friston, Brown, Frackowiak, & Dolan, 1993). Increases in PFC activation, particularly the left dorsolateral region are associated with symptom reduction (Kennedy, Eisfeld, Meyer, & Bagby, 2001).

Hypoactivation of the dorsal region of the ACC is associated with depression, and increased activity in this area has been found to coincide with successful antidepressant treatment (Bench, Frackowiak, & Dolan, 1995; Buchsbaum et al., 1997). In contrast, the rostral ACC tends to be hyperactive in depression but such hyperactivation predicts a positive treatment response (Mayberg et al., 1997).

Depression is often associated with hippocampal atrophy, as evidenced by myriad MRI studies (Bremner et al., 2002; Mervaala et al., 2000; Sheline et al., 1999; Sheline et al., 1996; Steffens et al., 2000). PET studies show decreased resting glucose metabolism in the hippocampus (Saxena et al., 2001). Atrophy and hypometabolism in particular brain areas may reflect a decrease in glial cells in addition to neuronal shrinkage or loss. A number of studies have found a disturbance in glial cells in individuals with depression, particularly in the prefrontal cortex (Ongur, Drevets, & Price, 1998). Since glial cells modulate neural metabolism and release trophic factors, loss of glial cells may contribute to a wide range of neuronal dysfunction, including decreased neurogenesis, synaptogenesis and neuronal death.

Imaging studies of depressed individuals have shown CBF to be pathologically increased in areas that are thought to mediate emotional stress responses (posterior orbital cortex and the amygdala). Conversely, CBF is typically decreased in areas related to attention (dorsal anterior cingulate). For a review, see Davidson, Pizzagalli, Nitschke, & Putnam, (2002). The amygdalar hyperactivation seen in depression is decreased to normal levels by antidepressant medication in line with symptom reduction, especially for those with trait negative affect and anxiety (Davidson et al., 2002).

Frontal Asymmetry

Functional brain abnormalities in depression often appear to be asymmetrical, especially in frontal regions. Specifically, the left frontal region appears to be less active than the right side, as inferred by electroencephalographic alpha band activity. For reviews on frontal asymmetry and affective style, see Allen, Coan & Nazarian (2004) or Coan & Allen (2004). Individuals with high scores on the Beck Depression Inventory (Schaffer, Davidson, & Saron, 1983) and individuals who were clinically diagnosed with depression (Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1991) showed greater right-than-left frontal activity, although some studies failed to yield this finding (Reid, Duke, & Allen, 1998). Moreover, this pattern is found in euthymic individuals with history of depression (Allen, Iacono, Depue, & Arbisi, 1993; Gotlib et al., 1998; Henriques & Davidson, 1990), suggesting that frontal asymmetry may index a diathesis towards depression (Allen, Urry, Hitt, & Coan, 2004; Coan & Allen, 2004). This diathesis may reflect, in part, that frontal asymmetry is also predictive of reactions to emotionally evocative situations. For example, Wheeler, Davidson, & Tomarken (1993) found that individuals with relatively greater left frontal activity reported less intense negative affect to negatively valenced films than individuals with relatively greater right activity, but reported more intense positive affect in response to positively valenced films. Davidson (2000) proposed that the left-sided frontal hypoactivity represents a deficit in the approach/appetitive motivation system, or " a neural reflection of the decreased capacity for pleasure, loss of interest and generalized decline in goal-related motivation and behavior" (p 98). Consistent with this theoretical framework, relatively

greater left frontal activity is related to trait-like dispositions hypothesized to reduce risk for depression, such as behavioral activation sensitivity (Coan & Allen, 2003; Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997) and greater right frontal activity is related to psychopathology including not only depression, but also panic disorder, (Wiedemann & Pauli et al., 1999) and anxiety (Davidson et. al., 2000).

Neuropsychological findings

Neuropsychological tests of individuals with depression yield deficits that are consistent with dysfunction in brain areas believed to be disturbed in depression, specifically, the hippocampus, anterior cingulate, prefrontal cortex and amygdala. Perhaps because of the neurotoxic effects of cortisol and IL-1, and trophic factor dysregulation in the hippocampus and PFC, depression is associated with a type of memory disturbance that reflects hippocampus-specific impairment and amygdalar hyperactivation. Hippocampal deficits are reflected by impaired recall of specific verbal episodic material (i.e. autobiographical memory) (Wolkowitz, Reus, & Weingartner, 1990) and spatial memory related to contextual cues (Arbel, Kadar, Silberman, & Levy, 1994; Aubert et al., 1995). While on one hand, high levels of cortisol have been shown to impair explicit verbal memory (Newcomer et al., 1999) and the specific details of life events, they has also been shown to enhance memory for negatively valenced emotional material (Buchanan & Lovallo, 2001). The result is emotionally thematic, overgeneral "narrative smoothing", a process by which preserved fragments of memory are woven into a theme that may be true to the gist of the experience but inaccurate for the details (Burke, Heuer, & Reisberg, 1992; Heuer & Reisberg, 1990).

This particular pattern of memory impairment is common in depression. For example, depressed individuals often substitute memories of specific events with overgeneral autobiographical memories that summarize events over repeated occasions (Williams, 1996). Overgeneral memory is associated with difficulty imagining the future in a specific (usually positive) way, as well as hopelessness (Williams et al., 1996), and a poorer prognosis (Brittlebank, Scott, Williams, & Ferrier, 1993; Williams, Teasdale, Segal, & Soulsby, 2000). This type of memory impairment, where the gist is remembered but the specific details are forgotten, is consistent with a relative imbalance between the hippocampus and the amygdala, where the hippocampus is impaired and the amygdala is hyperactive (Payne, Britton, Nadel, & Jacobs, 2004).

Attentional and memory biases for negatively valenced material in depression are thought to be related to the hyperactivity of the amygdala, which may be facilitated by cortisol (Ferry, Roozendaal, & McGaugh, 1999). Hyperactivation of the amygdala is thought to account for the tendency of depressed individuals to ruminate about negative memories (Cahill, 2000) and show a selective recall for negatively valenced stimuli over neutrally or positively valenced stimuli (Drevets, 2001).

While hippocampus and amygdala dysregulation lead to memory disturbances in depression, dysregulation of the prefrontal cortex leads to deficits in executive function. Depressed individuals tend to be impaired on tests of working memory (digits backward) and cognitive set shifting (Trails B, digit symbol substitution) (Austin, Mitchell, & Wilhelm, 1999). The brain areas that are related to attention (dorsal ACC), set shifting

and working memory (dorsolateral PFC) are typically hypoactive in depression (Austin et al., 1999).

Trait and State-like Abnormalities and Progressive course of Illness

Many of the neurophysiological abnormalities that are associated with depression, including NE disturbance, increased REM density and REM sleep latency, poor sleep maintenance, hypercortisolism, suppressed specific immunity, limbic hyperactivity, and anterior hypoactivity (especially left) are considered state-dependant abnormalities. In earlier episodes, these changes often occur in response to sustained stress, coincide with or precipitate depressive symptomology and subside upon remission (Thase et al., 2002). However, there is evidence that these abnormalities may become less and less stress and depression-dependent as episodes progress. That is, these disturbances may continue to linger despite clinical improvement and are associated with residual symptoms and increased risk for relapse.

For example, depression-related prefrontal cortex dysfunction does not always return to normal when depression remits. Specifically, greater right frontal electroencephalographic asymmetry (Henriques & Davidson, 1990) and executive dysfunctions like set-shifting difficulties (Paradiso, Lamberty, Garvey, & Robinson, 1997) have been found to remain in the absence of depressive symptomatology. In addition, many sleep abnormalities, including decreased REM sleep latency, increased REM density and decreased slow-wave sleep persist for months after clinical remission (Rush et al., 1986; Steiger, von Bardeleben, Herth, & Holsboer, 1989). The persistence of a short REM sleep latency, which is believed to have both state and trait aspects, has been

associated with an increased risk for relapse (Giles, Jarret, Roffwarg, & Rush, 1987). Sleep disturbance itself is a major risk for relapse, as insomniacs are 4 times more likely to become depressed than good sleepers (Breslau et al., 1996). Low vagal tone that persists into remission is also associated with increased relapse and poorer prognosis (Balogh et al., 1993; Khaykin et al., 1998). Similarly, overgeneral memory persists into remission and negative emotional biases can be reactivated in times of transient negative mood or stress (Williams et al., 2000). Negative reactions to transient moods tend to prolong the negative mood by increasing recall of negative events and attention to negative stimuli, therefore increasing the risk of relapse. The HPA axis and cortisol reactivity may also continue to be disturbed in remission. Although cortisol levels often return to normal levels (Steiger, 2003), cortisol reactivity tends to be blunted in formerly depressed vs. never-depressed individuals (Brown, 2001). There is presently much discussion and research about whether these various manifestations of biological "kindling" or accumulating sensitization may explain why later episodes may become progressively more independent of precipitating stressors and are apparently more endogenously produced (Hammen, 2005; Kendler et al., 2000; Monroe & Harkness, 2005; Post, 1992; Post et al., 1984).

Heritable trait-like abnormalities, including decreased SWS, reduced REM sleep latency, and decreased 5-HT neurotransmission may also play a role in the kindling phenomenon, as they are associated with earlier onset and greater vulnerability to recurrence (Thase et al., 2002). Individuals with these heritable risk factors, or certain gene polymorphisms (Caspi et al., 2003) may require fewer or milder stressful events to

precipitate depressive episodes, as their biology is considered "pre-kindled", or similar to the biology of those who have already had several episodes (Kendler, Thornton, & Gardner, 2001). Because of the progressive sensitization of biological disturbances lends itself to the acceleration of recurrent episodes which become more and more difficult to treat, it has been suggested that effective interventions must "dampen more directly pathological circuits or activate compensatory circuits" (Thase et al, 2002, p 211).

In summary, the neurophysiological concomitants of depression resemble those found following chronic stress, first in a state-dependent way, then taking on a more persistent and progressive presence. Depression is associated with a hyperactivation of the sympathetic stress response system, as manifested by enhanced HPA, amygdala and REM sleep activity, and increased levels of acute phase proinflammatory cytokine and cortisol. At the same time, parasympathetic influences are reduced in depression, as evidenced by reduced slow-wave sleep and lower vagal tone. Disruptions of modulating influences of the stress response system, such as NE and 5-HT, contribute to or perhaps exacerbate the sympathetic/parasympathetic imbalance.

The result of chronic HPA overdrive is likely an impairment in growth and plasticity in brain areas related to emotion, memory and attention. Reversal of many of these disturbances, via medication or other methods, ameliorate depressive symptoms.

The Reversal of Depression-Related Abnormalities By Meditation

The following section reviews studies that suggest that mindfulness and other related forms of meditations may be able to reverse a number of these depression-related abnormalities. Normalization of these systems may provide a potential mechanism for the

success of mindfulness-based depression relapse prevention, as well as improvement of depressive symptoms in various populations.

Description of Mindfulness

The concept of mindfulness originated in India about 2500 years ago as part of Theravada and Mahayana Buddhist meditation practice. The concept and practice have been adopted in the U.S. not only as part of Buddhist communities, but also as therapeutic interventions in clinical settings. Jon Kabat-Zinn created an 8-week psychoeducational program called Mindfulness-based Stress Reduction (MBSR). More recently MBSR has been tailored as a maintenance program to prevent depressive relapse in a program called Mindfulness-Based Cognitive Therapy (Segal, Williams, & Teasdale, 2002).

Within the context of meditation, a typical session of formal mindfulness meditation has been described as follows (Bishop et al., 2004):

> The client maintains an upright sitting posture, either in a chair or cross-legged on the floor, and attempts to sustain attention on a particular focus, most commonly the somatic sensations of his or her breathing. Whenever attention wanders from the breath to inevitable thoughts and feelings that arise, the client will simply take notice of them and then let them go as attention is returned to the breath. This process is repeated each time that attention wanders away from the breath. As sitting meditation is practiced, there is an emphasis on taking notice of whatever the mind

> happens to wander to and accepting each object without making judgments about it or elaborating on its implications, additional meanings or need for action (p 232).

Additional forms of formal mindfulness meditation may include the practice of mental noting or labeling the transient contents of the mind (Goldstein, 2003; Nhat Hanh, 1987). For example, a meditator may gently say "breathing in, breathing out" in synchrony with the breath, or note "anger" or "agitation" as it arises and passes away. Formal mindfulness practice is often extended to activities like walking, or gentle stretching. Both the MBSR and MBCT programs employ formal as well as "informal" mindfulness practice which includes shorter (1-3 minute) periods of intentional present-moment awareness (Kabat-Zinn, 1990; Segal et al., 2002).

Meditation and Mood Disturbance

More than 15 studies have found that mindfulness and other meditation-based interventions are associated with statistically significant decreases in depressive symptomatology in both clinical and non-clinical populations (Astin, 1997; Astin et al., 2003; Bedard et al., 2003; Gross et al., 2004; Kabat-Zinn, Lipworth, & Burney, 1985; Kabat-Zinn et al., 1992; Klein et al., 1985; Kristeller & Hallet, 1999; Reibel, Greeson, Brainard, & Rosenzweig, 2001; Roth & Robbins, 2004; Sagula & Rice, 2004; Shapiro, Schwartz, & Bonner, 1998; Sheppard, Staggers, & John, 1997; Smith, Compton, & West, 1995; Speca, Carlson, Goodey, & Angen, 2000; Tloczynski & Tantriella, 1998; Waelde, Thompson, & Gallagher-Thompson, 2004). See table 2 for summary.

One meditation intervention study selected participants specifically for the treatment of acute depression (Klein et al., 1985). Medication-free individuals who met Research Diagnostic Criteria (RDC) for unipolar depression were randomly assigned to either a running, group psychotherapy or a meditation condition for 2 hours a week for 12 weeks. The meditation condition was intended to be a body-focused control condition without the aerobic components of running, and consisted of silent sitting, breath awareness and yoga-based stretching. Group therapy included components of interpersonal and cognitive therapy. Meditation and running, but not the psychotherapy condition, showed significant improvements in Cornell Medical Index depression and inadequacy scores, after 12 weeks, with sustained improvement after 9 months. While the running condition outperformed the other conditions in terms of improvement in Role Rating Questionnaire (RRQ) self-concept scores, both running and meditation showed significant improvements in Social Adjustment Self-report Questionnaire (SAS) self-esteem scores, but only meditation maintained this improvement at follow-up. The meditation condition, but not running or psychotherapy, also showed significant improvements in SCL-90 social adjustment, anxiety and tension at post-treatment. All three treatments showed significant improvements in depression according to self report scores and clinician assessment (HAM-D and Global Assessment Scale), so that nearly 90% of completers in all groups scored below the moderate-to-severe depression range. Percent improvement in SCL-90 depression in the running, meditation and psychotherapy conditions were 55%, 68% and 41% respectively, which represents a clinically significant response for running and meditation. Percent improvement in vegetative

symptoms (poor appetite/overeating, sleep onset or maintenance difficulties, early morning awakenings, thoughts about death, guilt) showed a similar pattern (running 49%, meditation 67%, psychotherapy 31%). Thus, although all groups showed improvements in depression, meditation and running seemed to have a slightly more favorable and clinically significant outcome on depression than group psychotherapy, especially at follow-up. Sustained symptom improvement was associated with continued running or meditation practice.

Although not purposely targeting depressed populations, several other studies included participants with mean baseline depression scores that indicated clinically significant levels of depression on well-validated assessment instruments (Astin et al., 2003; Bedard et al., 2003; Kabat-Zinn et al., 1992; Kristeller & Hallet, 1999; Sagula & Rice, 2004; Speca et al., 2000; Waelde et al., 2004).

In a randomized controlled clinical trial, a heterogeneous sample of cancer outpatients (n=90) with clinically significant levels of depression was randomly assigned to a 7-week MBSR class or waitlist condition (Speca et al., 2000). MBSR completers showed a significantly greater improvement in POMS anxiety (49% vs. 5%), depression (44% vs. 3%), anger (41% vs. 1%), vigor (30% vs. 2%), confusion (45% vs. 6%) and total mood disturbance (65% vs. 6%) than controls, although neither group showed changes in fatigue. The meditation group also showed significantly greater reduction in emotional irritability (39% vs. 12 %) and total stress scores (31% vs. 11%) than controls.

In a study by Kabat Zinn et al. (1992), 20 patients who met criteria for DSM-III-R criteria for anxiety or panic disorder completed the 8-week MBSR course. Although the

target population was anxiety and panic disorders, many of subjects also had clinically significant levels of depression with scores indicating moderate to severe levels of depression (initial HAM-D score=33, initial BDI score =18.8). Anxiety, panic and depression levels were assessed at 4 time points (initial recruitment, pre-treatment, post-treatment and 3 month follow-up) with both clinician rated (Hamilton Rating Scales for Anxiety and Depression, Structured Clinical Interview) and self-rated (Beck Anxiety and Depression Inventories) assessments. Both Anxiety and depression scores decreased significantly from pre-treatment to post-treatment, with improvements maintained at 3-months post-treatment. However, this study did not have adequate control group to conclude that the improvements were treatment-specific.

In a study by Astin et al. (2003), 128 patients with fibromyalgia and clinically significant levels of depression (mean BDI=16.7) were randomized into a mindfulness meditation/Qigong or education/support control condition. While BDI scores dropped significantly, gains were similar for both groups. In a single group extended baseline design, 18 individuals with binge eating disorder and clinically significant baseline depression scores (BDI= 17) showed a 48% reduction in BDI scores following 6 weeks of MBSR (Kristeller & Hallet, 1999). Meditation practice was correlated (r=.60) with reduction of depression scores. In a study by Sagula & Rice (2004), 39 individuals with chronic pain and clinically significant levels of depression (BDI short form=9) were non-randomly assigned to a MBSR or waitlist control condition. The MBSR group was associated with significantly greater reductions in BDI scores than controls.

In a clinical case series of individuals with traumatic brain injury (TBI), individuals with concurrent DSM-IV disorders or suicidal ideation were excluded (Bedard et al., 2003). However, the baseline BDI-2 score (18.4) indicated clinically significant levels of depression. The 10 individuals that completed a 12 week MBSR course showed a significant decrease in BDI-2 scores, especially on the cognitive/affective domain. Depression scores increased for 3 dropouts that agreed to serve as controls, generating a nearly significant time x group interaction (p=.059). However, the self-selected control group is not adequate to make strong conclusions. Other clinical interventions studies that excluded DSM disorders have also found significant reductions in depression scores (Carlson et al., 2003), but some have not (Shapiro, Bootzin, Figueredo, Lopez, & Schwartz, 2003; Surawy, Roberts, & Silver, 2005), perhaps due to truncated baseline levels.

In a second clinical case series, 12 female dementia patient family caregivers with clinically significant levels of depression participated in a 6-session yoga-meditation program called "Inner Resources" (Waelde et al., 2004). The program, which is similar to MBSR, included daily practice of breath and mantra meditation, guided imagery and gentle stretching (hatha yoga). CES-D depression symptoms dropped significantly, yielding a large effect side (d=1.02). Minutes of practice per week was strongly correlated with decrease in depression scores (r=.62). Again, the absence of a control group limits conclusions about treatment specificity. In a third clinical case series, 121 individuals from a heterogeneous patient population (16% with depression) who

completed a MBSR course showed a 34% reductions in SCL-90 depression (34%) and anxiety (44%) that were maintained at 1-year follow-up (Reibel et al., 2001).

In other clinical studies, baseline levels of depression and changes in depression were more difficult to determine because they were either not measured, not published or the scales used were less standardized to determine clinical cutoffs. After 8 weeks of MBSR, subjects with chronic pain (N=90) reported a 55% reduction in POMS total mood disturbance and "significant mean reductions in all dimensions of the SCL-90" (Kabat-Zinn et al., 1985). A subset of 21 MBSR participants who were referred from the pain clinic was compared to 21 pain clinic non-MBSR patients. The MBSR group showed significantly higher reductions SCL-90 subscales, including depression (59% vs. 18%), Anxiety (65% vs. 29%), Hostility (57% vs. 7%), Sensitivity (i.e. low self-esteem, 45% vs. 34%) than pain clinic treatment. Since only change scores were published, baseline depression levels could not be determined. In a heterogeneous bilingual patient sample where 50% had a diagnosis of major depression, MBSR was associated with greater reductions in fatigue and role impairment caused by emotional problems than a self-selected comparison group that could not participate due to scheduling conflicts (Roth & Robbins, 2004).

In addition to clinical populations, meditation is associated with improvements in depressive symptoms in non-clinical populations. In a study by Smith (1995), 36 undergraduate volunteers who received extra credit were randomly assigned into Fordyce's Personal Happiness Program (PHEP), with/ or without meditation (MHEP) or a education/discussion passive control group. Active groups met twice a week for 1.5

hours for 6 weeks. The Meditation/Happiness group practiced a concentrative form of meditation (Relaxation Response) with the mantra "peace" synchronized with the breath. The addition of meditation improved the happiness program on all measures including increased happiness (Happiness Measure Fordyce 1988; Psychap Fordyce 1986), depression and state and trait anxiety. BDI scores dropped 9.6 points for the meditating/happiness group, and 4.47 points for the happiness program without meditation, and did not change for the control group. Effect size for improvements in depression by the addition of meditation vs. the happiness program only was calculated to be 1.02 (i.e. large).

Similar undergraduate volunteers who were randomly assigned to MBSR condition showed a significantly larger reduction in SCL-90 depression (59% vs. 7%), anxiety (60% vs. 10%) and vegetative symptoms (73% vs. 2%) than a passive control condition (Astin, 1997). Because baseline scores were not published, it is impossible to determine the pre-treatment level of depression or the extent to which percent reductions were inflated by low baseline disturbances. In medical students with subclinical levels of depression, Shapiro, Schwartz & Bonner (1998) found smaller SCL-90 depression reductions (about 34%) after MBSR compared to an increase (about 15%) in waitlist controls. In another college sample, Tloczynski & Tantriella (1998) randomized undergraduates into a Zen breath, relaxation or education control condition, and used the College Adjustment Scale (CAS-d) to indicate depressive symptoms. Both meditation and relaxation showed significant improvements in depressive symptoms over the control condition, while meditation outperformed relaxation on improvements in interpersonal

difficulty scores. In another randomized control trail in a non-clinical population, Davidson et al. (2003) randomly assigned 41 Biotech employees to MBSR or a waitlist control condition. The MBSR group showed significantly greater reductions in the PANAS trait negative affect scale, although the scores were not published.

In addition to improving mood disturbances in a wide range of populations, mindfulness training has been found to dramatically reduce the rate of relapse. Teasdale et al. (2000) randomly assigned 145 formerly depressed individuals to an 8-week MBCT program or to continue with treatment as usual (TAU). After 60 weeks, individuals with 3 or more episodes of depression who had at least 4 session of MBCT had nearly half the relapse rate of individuals who had continued their usual treatment. In the TAU group, there was a positive linear relationship between number of previous episodes and likelihood of relapse/recurrence, so that more episodes predicted higher rates of relapse. In the MBCT group, however, no such relationship was found, which suggests that the intervention may impede the progressive "kindling" effect that is typical of recurrent depression. MBCT was most effective for individuals with more recurrent forms of depression, which are typically more difficult to treat, and are more vulnerable to relapse. Given that the likelihood of relapse exceeds 80% with an average of four 20-week episodes over a lifetime (Judd, 1997; Paykel et al., 1995), this reduction in relapse is a significant contribution to treating the potentially lifelong disease of depression. These findings were more recently replicated by the same group (Ma & Teasdale, 2004), but await independent replication.

While it is believed that meditation-based or psychotherapy interventions may not be suitable for the treatment of acute depression because of compromised executive and attention systems (Segal et al., 2002; Thase et al., 2002), these findings suggest that meditation may be useful in patients who are not in remission, or have clinically significant levels of depression. The next section reviews evidence that meditation may counteract many of the physiological abnormalities that are found in depression, which may add to its antidepressant potential.

Insert table 2 about here

The Physiological Effects of Mindfulness

While most theories about the effect of mindfulness training on depression are cognitive (Brown & Ryan, 2003; Teasdale et al., 2002; Teasdale, Segal, & Williams, 1995), a few studies suggest that mindfulness training may evoke physiological changes that reverse those seen in depression.

Mindfulness and Stress

A number of studies have shown that subjective indices of stress are decreased following mindfulness-interventions (Beddoe & Murphy, 2004; Carlson, Speca, Patel, & Goodey, 2003, , 2004; Carlson, Ursuliak, Goodey, Angen, & Speca, 2001; Chang, Palesh, & Caldwell, 2004; Gross et al., 2004; Tacon, McComb, Caldera, & Randolph, 2003; Williams, Kolar, Reger, & Pearson, 2001), although few physiological measures of stress have been performed. A recent study of MBSR within the context of a therapeutic treatment community for substance abuse found that salivary levels of the stress hormone cortisol dropped significantly ($p<.0001$) following the program (Marcus, Fine, &

Moeller, 2003). Similarly, Carlson, Speca, Patel, & Goodey (2004) found that cortisol profiles normalized in cancer patients, following MBSR. This study also investigated an additional anti-stress marker DHEAS, but found no change after MBSR in this (non-depressed) population. These findings suggest that mindfulness meditation reduces physiological stress reactivity associated with the HPA axis. Further studies of mindfulness with additional physiological indices of stress (nitric oxide, NE, DHEAS, prolactin, cortisol reactivity) in populations selected for depression are needed.

Mindfulness and Melatonin:

Melatonin has been considered an anti-stress, pro-health hormone because it induces sleep (Zhdanova et al., 1995), inhibits vascular reactivity (Monroe & Watts, 1998), increases growth hormone (Valcavi, Zini, Maestroni, Conti, & Portioli, 1993), activates the immune system (Maestroni & Conti, 1990) and counteracts the immunosuppressive effects of stress (Maestroni, 1993). Although a recent study failed to find an effect of mindfulness on melatonin levels in cancer patients (Carlson et al., 2004), others have shown that baseline overnight melatonin levels are increased in mindfulness meditators vs. non-meditators (Massion, Teas, Hebert, Wertheimer, & Kabat-Zinn, 1995).

Mindfulness and the Immune system:

As described earlier, many depressed individuals show suppression of specific immunity (natural killer activity, antibodies) compared to non-depressed individuals. In a study by Davidson et al., (2003), specific immunity was found to increase following an MBSR program. At the end of the course, subjects were given an injection of an influenza vaccine and blood samples were taken at 4 and 8 weeks post-injection.

Meditation subjects showed a greater increase in influenza antibody titers between the two blood samples. Increases in left anterior brain activation were directly correlated with the immune response magnitude.

Similarly, in a study of HIV-infected individuals (Robinson et al., 2003), NK activity and cell number were found to be significantly increased from baseline and non-treatment controls after an 8-week MBSR program. These immune changes were maintained at 3 months post-intervention and were correlated with self-reported decreases in depression, anger, confusion and total mood disturbance.

In a study of cancer patients (Carlson et al., 2003), MBSR was found to have a number of effects on immune parameters that "are consistent with a shift in immune profile from one associated with depressive symptoms to a more normal profile"(Carlson, p 571). A significant decrease in proinflammatory cytokine IFNγ and a greater than three-fold increase in the anti-inflammatory cytokine IL-4 following MBSR was observed. According to Carlson, this pattern of immune changes is consistent with a shift away from a pro-inflammatory response to an anti-inflammatory environment. While the study also found a small but significant decrease in anti-inflammatory cytokine IL-10, Carlson points out that this cytokine has been positively correlated with depressive symptoms in cancer patients. This study is the first to investigate the effects of mindfulness-based intervention on pro-inflammatory cytokines and has yielded promising results. Future studies in other, non-cancer, samples may be able to distinguish MBSR's effects on depression versus disease-related immune compounds.

Frontal Asymmetry

As described earlier, depressed individuals often have greater right than left frontal brain activity compared to non-depressed individuals. In a recent study (Davidson et al., 2003), increases in relative left central activity were found following a MBSR course. EEG measures were recorded before and after an 8-week mindfulness meditation course taught by Jon Kabat-Zinn. Subjects in the meditation group showed a greater increase in left-sided resting brain activity than controls across central (C3/C4) regions. In comparison to controls, meditation also produced a significant increase in left-sided brain activity across "anterior temporal" regions (T3/T4) in response to positive emotion induction. While the area with the largest post-meditation shift in asymmetry (C3/C4) is not traditionally associated with affective disposition, Davidson (2003) reports that his lab has found "reliable affect-related asymmetries in the past" (p 569) in this area. His conclusion that "meditation can produce increases in left-sided anterior [activity] that are associated with reductions in anxiety and negative affect and increases in positive affect" (p 569) certainly suggests applications for use of meditation with depression.

However, because the subjects in this study were drawn from a non-clinical sample of non-depressed, healthy volunteers, the effect of meditation on the frontal asymmetry in individuals with depression or a history of depression is still unknown. A replication of this study with depressed or remitted individuals, who ostensibly would have greater right-sided anterior activity at baseline, is needed.

Mindfulness and Overgeneral Memory

Although not a physiological measure per se, performance on memory tasks can reflect the integrity and functioning of brain systems that underlie memory. As described

earlier, depression is associated with impaired hippocampal and prefrontal functioning with an overactivation of the amygdala. This pattern of brain activation is also associated with a specific pattern of memory disturbance -- overgeneral (gist-based) autobiographical memory. In a recent study, MBCT was found to reverse the overgeneral autobiographical memory deficits of formerly depressed individuals (Williams et al., 2000). Given that meditation has also been found to increase activation in the hippocampus and PFC (see below), this finding suggests that mindfulness may reverse the depression-related dysfunction in these areas.

Mindfulness and attention

Meditation may improve the ability to sustain attention. For example, one study compared concentration meditators to mindfulness meditators and found that both groups showed better attention in comparison to non-meditator controls on an auditory perception test, but that the mindfulness group did better than both groups at faster speeds (Valentine & Sweet, 1999). Again, although not a direct measure of brain function, increased attentional ability among meditators suggests that meditation may alter the functioning of brain areas that underly attention, in particular the anterior cingulate and the prefrontal cortex. In addition, this study indicates that different forms of meditation may have differential effects on these brain areas and their associated functions.

Mindfulness and Neurogenesis and Plasticity:

Changes in frontal asymmetry and correction of depression-related memory biases following mindfulness training suggest that this form of meditation may affect neural circuitry. Davidson has previously described how the PFC, amygdala,

hippocampus (the areas most consistently affected in depression) are the areas of the brain that are most malleable to environmental influence (Davidson, Jackson, & Kalin, 2000) and suggests that intentional systematic training in meditation may alter neural connectivity in these areas (Davidson et al., 2000; Davidson et al., 2003; Lutz, Greischar, Rawlings, Ricard, & Davidson, 2004). According to Davidson, his finding of shifted EEG asymmetry after MBSR implies that mindfulness meditation can induce changes in neural connectivity (Davidson et al., 2003). He makes similar statements about a recent study that found increased gamma oscillations in experienced Tibetan meditators vs. American undergraduate novices (Lutz, Greischar et al., 2004).

There is also perhaps more direct evidence that suggests that meditation may increase both neuronal and synapse growth. A cross-sectional structural MRI study (Lazar et al., 2005), for example, found a strong positive correlation between meditation experience and cortical thickness in a number of brain areas. Increased years of meditation were associated with greater cortical thickness. Most relevant to the proposed role of mindfulness in helping depression by preventing neural loss and/or promoting growth was the finding that meditation prevented age-related thinning of the pre-frontal cortex.

Whether mindfulness or any form of meditation can alter trophic factors, dendritic arborization, birth of new neurons, or creation of new synapses is still unknown, mostly due to technological limitations. However, meditation related decreases in neurotoxic substances like pro-inflammatory cytokines and cortisol are a promising sign. Further

investigations of mindfulness, neurogenesis, synaptogenesis and changes in functional connectivity are undoubtedly an exciting direction for the future.

Mindfulness and Sleep

In the past few years even though there has been increased interest in the effect of mindfulness meditation as a treatment for sleep disturbance, there are relatively few studies. Of ten studies reported since 1998, eight have examined changes in the sleep of patients with secondary or comorbid insomnia and only two in primary insomnia. In many of the studies, the primary measures of sleep have been self-ratings of sleep quality and/or the Pittsburgh Sleep Quality Index (PSQI), an 18-item questionnaire.

In a randomly controlled trial, Shapiro et al. (2003) examined the effects of MBSR on the sleep of 63 women with breast cancer. There were no significant differences overall between the mindfulness group and a self-paced information control condition. Within the MBSR group, however, there was a significant relationship between the frequency with which mindfulness meditation was practiced and increased ratings of feeling refreshed after sleep. Carlson et al. (2003; 2004) in a non-randomized trial of patients with breast and prostate cancer also found that MBSR significantly improved sleep quality. In a subsequent clinical series with 63 patients with different types of cancer, Carlson and Garland (2005) found that MBSR resulted in broad-ranging improvement on sleep (measured by the PSQI) as well as on depression, fatigue, and stress (measured by the Profile of Mood States and the Symptoms of Stress Inventory). Improvement on all subscales of the PSQI (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime

dysfunction) were significant from pre to post MBSR. The proportion of the sample having a score higher than 5 (the cut point for poor sleep) was 90% at baseline and 79% post-MBSR; the proportion have a score higher than 10 (more severe sleep disturbance) was 51% at baseline and 27% post MBSR.

In a non-randomized pilot study with a different patient group, Gross et al. (2004) found that 20 organ transplant patients reported improved sleep on the PSQI after 8 weeks of MBSR and at 3-month follow-up. The proportion of the sample having a score higher than 5 was 80%, 53%, and 47% at baseline, post-MBSR, and follow-up.

In addition to the results from evaluations focusing on MBSR as a single intervention, programs that integrate mindfulness meditation with other techniques have been found to improve symptoms in clinical populations. Cohen et al. (2004) in a randomly controlled trial with lymphoma patients, examined the effects of mindfulness and Tibetan yoga, which is similar to the "mindful movement" portions of MBSR that emphasize breathing. The investigators found improved subjective sleep quality, shorter sleep onset latency, longer sleep duration and less use of sleep medications, as reported on the PSQI for the patients receiving the intervention compared to those in a wait-list control condition. Singh, Berman, Hadhazy, and Creamer (1998) conducted a pilot study that combined cognitive behavioral therapy, mindfulness meditation, and qigong movement therapy for 28 fibromyalgia patients. They found significant improvements across a number of measures including sleep as measured by a 100-mm visual analog scale evaluating "How much of a problem is sleep?" and on the sleep factor of the BDI.

In addition significant improvement was reported on fibromyalgia symptoms, other BDI factors, and health behaviors as measured by self-report questionnaires.

Further, Bootzin and Stevens (2005) designed a combined cognitive-behavioral and mindfulness intervention for adolescents with sleep and daytime sleepiness problems who had been in treatment for substance abuse. In preliminary analyses of 55 teens comparing those who completed four or more of the six treatment sessions with those who did not, the 23 completers showed significant reductions in sleep disturbance on daily sleep diaries (including sleep efficiency, sleep onset latency, number of awakenings, total sleep time, and ratings of sleep quality). Home actigraphy showed trends confirming these findings for sleep onset latency and total sleep time. Dim light melatonin onset (DLMO) analyzed from saliva collected during a lab night before and after the intervention showed a trend for noncompleters to have increased phase delays from pre to post-treatment while completers maintained the degree of phase delay they exhibited at baseline (Hasler, Cousins, Fridel, Wenk, & Bootzin, 2005).

There have been encouraging pilot studies examining the effectiveness of MBSR and MBCT with patients having primary insomnia. Shapiro, Britton, Penn, & Bootzin (2003) found that MBSR produced significantly improved wake after sleep onset (WASO) on sleep diaries, worry (Penn State Worry Questionnaire), and depression (BDI) in 7 females insomniacs. Heidenreich, Tuin, & Pflug (2004), in a study of MBCT with 12 patients having primary insomnia found significantly improved total sleep time and sleep latency on sleep diaries and worry (Thoughts Control Questionnaire Insomnia), and depression (BDI).

Full overnight polysomnographic (PSG) sleep studies, the gold standard of objective sleep measures, were not used to evaluate the outcome of mindfulness interventions in any of the above studies. Overnight PSG would allow for objective measurement of many depression-related sleep variables, such as REM latency and density, amount of slow-wave sleep, as well as sleep disturbance that is difficult to measure through subjective questionnaires, such as microarousals. Early results from the first study using PSG (Britton, Fridel, Payne, & Bootzin, 2005) have been reported for MBCT for 14 partially remitted depressed patients, 8 of whom had PSG sleep efficiency below 90%. Patients with poor sleep efficiency at baseline had significantly decreased microarousals and trends for decreases in stage 1 minutes and decreased number of awakenings after treatment. Sleep diaries for the entire sample showed a significant increase in sleep efficiency following MBCT. Depression (BDI) decreased significantly from baseline to post-treatment. Improvement in sleep efficiency (from sleep diaries) was significantly associated with improvement in depression (r=.66).

Physiological Effects of Other Forms of Meditation

There have only been a handful of studies on mindfulness training that have physiological endpoints. The advent of mindfulness as a therapeutic technique has just begun to flourish, with some of the most important studies still underway, in press, or remaining to be done. However, additional studies have been performed on the physiological effects of other related forms of meditation, and a review of these may provide potential physiological mechanisms and future directions for understanding mindfulness meditation's antidepressant effects.

Introduction to Transcendental Meditation

Transcendental Meditation (TM) is a Vedantic (Hindu) meditation technique in which a Sanskrit word or phrase is repeated in synchrony with the breath. A more Westernized version of TM with English words or phrases was created by Harvard cardiologist Herbert Benson and renamed "The Relaxation Response" (RR) (Benson, 1975). Similarly, other groups have modified TM to fit into non-religious medical contexts (Solberg et al., 2004).

While TM/RR and mindfulness meditation both include sitting quietly, adopting a passive, non-judgmental attitude and using a mental focusing device (usually the breath with or without a repeated phrase or mantra), the purpose of introducing TM in this paper is not to equate it with mindfulness. TM and mindfulness originated in different traditions (i.e. Hindu, Buddhist) with different theoretical orientations. However, TM has the largest empirical research base of any meditative tradition. While a handful of physiological studies have been conducted using mindfulness, hundreds have been conducting using TM. So far, many of the effects of these two types of meditation have been similar, in both physiological and mood-related ways. For example, both TM and mindfulness have been shown to reduce both psychological and physiological indices of stress and depression, including HPA axis hyperactivation (Carlson et al., 2004; Infante et al., 1998; Maclean et al., 1994), immune suppression (Carlson et al., 2003; Davidson et al., 2003; Robinson et al., 2003; Solberg, Halvorsen, Sundgot-Borgen, Ingjer, & Holen, 1995), and cardiovascular disturbances (Barnes, Treiber, Turner, Davis, & Strong, 1999; Barnes, Davis, Murzynowski, & Treiber, 2004). Thus, while studies of the physiological

effects of TM have to be replicated using mindfulness, TM-related effects on the physiological systems that are known to be implicated in depression may provide a framework for future investigations of mindfulness and depression.

TM and sympathetic stress indicators

TM's most depression-relevant effects revolve around its ability to reduce the physiological concomitants of acute and chronic stress. TM has been shown to consistently reduce signs of sympathetic nervous system activity involved in the (fight-or-flight) stress response. Moreover, TM has been repeatedly associated with reductions in HPA activation, most commonly reductions in cortisol and ACTH (Bevan, 1980; Jevning, Wilson, & Davidson, 1978; Maclean et al., 1994; Michaels, Parra, McCann, & Vander, 1979; Sudsuang, Chentanez, & Veluvan, 1991).

TM practice was also associated with decreases in other markers of sympathetic activity such as skin conductance and blood lactate levels (which increase with preparatory muscle tension) (Orme-Johnson & Farrow, 1977; Travis & Wallace, 1999). Meditators have been found to have increased skin resistance, decreased skin conductance and a faster recovery or habituation of the electrodermal response to stressful stimuli (Gaylord, Orme-Johnson, & Travis, 1989; Goleman & Schwartz, 1976; Travis & Wallace, 1999).

While many substances increase with stress, dehydroepiandrosterone sulfate (DHEAS) has been found to decrease with stress, as well as age and illness. A number of researchers, (Glaser et al., 1992; Walton, Pugh, Gelderloos, & Macrae, 1995) have found

that higher levels of DHEAS in TM meditators versus non-meditating controls, suggesting greater health and adaptability for meditators.

TM and Catecholamines

Circulating levels of catecholamines NE, epinephrine (E), and to a lesser extent DA, are considered classic indicators of the sympathetic stress response. Catecholamine dysregulation is also thought to be involved in the pathophysiology of depression, since drugs that increase extracellular NE and DA have antidepressant properties. The catecholamine and meditation literature highlights the aforementioned complexity of neurotransmitters systems and oversimplification of using absolute levels of neurotransmitter (via peripheral metabolites) to reflect the activity of that system.

A number of studies on catecholamines support the idea that TM decreases sympathetic output. Walton et al. (1995) found that TM practitioners had lower levels of catecholamine metabolite vanillicmandelic acid (VMA) compared to non-meditating controls. Similar reductions of VMA after TM practice were found in populations with abnormally high levels (Bujatti & Rierderer, 1976). More recently, Infante et al. (2002) found decreased levels of catecholamines (DA, NE, E) in regular practitioners of TM. In addition, the TM group showed no diurnal variation when catecholamine levels were measured at different times of day. Because self-reported anxiety levels did not differ between groups, the authors interpreted the lower levels of catecholamines to reflect "a lower hormonal response to daily stress" (Infante et al., 2002).

Other studies, however, do not show a straightforward reduction of catecholamines as an index of decreased sympathetic output. For example, Bevan (1980)

found no change in catecholamine concentration during TM, although other reductions in stress hormones such as cortisol were found. Lang, Dehof, Meurer, & Kaufman (1979) found higher levels of urinary catecholamines and plasma NE in advanced TM meditators in comparison with beginners. However, the same authors also found that NE failed to increase after exercise in the advanced TM group.

Benson (1983) found increased NE levels without an increase in heart rate or blood pressure in regular (twice daily for 30 days) practitioners of the Relaxation Response. He concluded that the Relaxation Response decreased physiological reactivity to NE (Benson, 1983). Mills, Schneider, Hill, Walton, & Wallace (1990) found that TM practitioners had lower levels of functional beta-adrenergic receptors (on lymphocytes) than non-practitioners. This finding supports Benson's hypothesis of decreased response to circulating levels of NE.

TM studies of hemodynamic functioning also support the idea that TM may reduce the body's response to NE. NE is a potent vasoconstrictor and elevations in blood pressure are thought to reflect both transient and chronic hyperactivity of sympathetic output. A number of studies have shown that TM causes decreases in blood pressure, both transiently (during meditation) (Barnes et al., 1999) and long-term, in both normotensives (Wenneberg et al., 1997) and patients with chronic high blood pressure (Alexander et al., 1996). In addition to mediation through NE, chronic sympathetic nervous system overactivity has also been implicated in elevating blood pressure by increasing atherosclerosis initiating factors like cholesterol and lipid peroxide. TM practitioners showed lower lipid peroxide levels and hypercholesterolemia (Calderon et

al., 1999). In general TM has been shown to be reduce health risks and mortality associated with sympathetic hyperactivity, particularly those found in cardiovascular diseases (Calderon et al., 1999; Zamarra, Schneider, Besseghini, Robinson, & Salerno, 1996).

Recently, Benson and colleagues have attempted to explain many of the Relaxation Response's effects through the actions of nitric oxide (NO), a multifunctional immune, vascular and neural signaling molecule (Stefano, Fricchione, Slingsby, & Benson, 2001). According to this theory, the Relaxation Response-induced increase in NO can thwart the acute stress response by counteracting the vasoconstrictive effects of NE and reversing the accumulation of pro-inflammatory cytokines. In a recent randomized controlled trial, the Relaxation Response was associated with increased concentrations of NO (Dusek et al., 2005). Given that individuals with depression have been found to have decreased levels of NO (Chrapko et al., 2004; Selley, 2004), future investigations of mindfulness meditation's effects on NO may be a rewarding avenue of investigation.

TM and serotonin

Meditation's effects on 5-HT also have mixed results. Three studies have found that TM increased 5-HT metabolite 5-hydroxy-3-indoleacetic acid (5-HIAA) following TM (Bujatti & Rierderer, 1976; Loliger, 1991; Walton et al., 1995). Solberg et al. (2004) found that baseline levels of 5-HT were higher in experienced meditators but decreased during meditation practice. A similar paradox has been found in the stress and depression literature in regard to 5-HT. While low baseline 5-HT levels in CSF have been

found in depression (Asberg et al., 1984), and 5-HT enhancing drugs improve depressive symptoms, 5-HT increases have also been found in response to acute stress (Malyszko, Urano, Yan et al., 1994). In addition, the 5-HT metabolite 5-HIAA should not be used as an index of serotonergic activity, as 5-HIAA levels sometimes decrease when extracellular 5-HT levels increase (Malyszko, Urano, Takada, & Takada, 1994). Thus, the study of absolute levels of 5-HT or 5-HT metabolites may not be the best correlate of "improvement" or "decline" in either stress or depression. Studies of receptor changes or other 5-HT -mediated brain changes, such as neurogenesis or synaptogenesis may be more promising.

TM and neuropsychological performance.

Again, although not a direct neurophysiological measure, neuropsychological tests of executive function and memory may reflect the integrity and functioning of brain systems that underlie attention (prefrontal cortex, anterior cingulate) and memory (hippocampus, basal ganglia, PFC), areas that are known to be impaired in depression. Some longitudinal studies have suggested that regular meditation practice is positively correlated with enhanced attentional capacity, as assessed by the Embedded Figures and Rod and Frame tests, as well as reports of decreased distraction by intrusive thoughts (Linden, 1973; Pelletier, 1974). A 12-week TM training in elderly participants showed improved performance on the Overlearned Verbal Task, a test that reflects cognitive flexibility and the ability to override overlearned information, two abilities that are thought to rely on the frontal lobes. The same study also found that TM training improved scores on the Associate Memory subscale of the Wechsler Memory Scale, a

task that may rely on the hippocampus (Brasted, Bussey, Murray, & Wise, 2003). In addition, an unpublished study found that minutes of meditation/day in a group of mixed-type meditators was correlated with decreased interference on the Stroop test and better performance on a global-local letter identification task compared to non-meditators (Chan, 2004). Other studies failed to find any effects of meditation on attention. Almost all of the neuropsychological studies to date have used samples of college students, and none have used samples where attentional ability is compromised or deficient. Future studies should continue with a longitudinal format to establish premeditation baselines, employ neuropsychological tests of executive function and memory with known neuroanatomical correlates, and use samples with known deficiencies in attentive and memory ability (i.e. depressed, ADHD etc). Increased attentional control and reduction in hippocampally-based memory impairments through mindfulness meditation has been hypothesized to be a key mechanism in preventing depressive relapse (Teasdale et al., 1995; Williams et al., 2000), although further research is needed to confirm this model.

TM and vagal tone:

As described earlier, depression is often associated with lower vagal tone and recovery from depression is correlated with increases in vagal tone. Vagal tone was found to be increased by Transcendental Meditation (Travis & Wallace, 1999) and therefore may be a candidate for a physiological mechanism of symptom improvement with mindfulness meditation.

TM and sleep

While most of the studies of meditation and sleep have used mindfulness interventions, one study using TM indirectly suggests that meditation may improve sleep quality by increasing the nighttime release of the somnogenic substance melatonin (Tooley, Armstrong, Norman, & Avni, 2000). Baseline levels of melatonin have also been found to be higher in meditators in comparison to non-meditators (Solberg et al., 2004). Melatonin increases are associated with increased slow-wave sleep, which is typically lacking in depression. Sleep loss is also associated with further immune disturbance and poor treatment outcome (Irwin, 2002). Thus, meditation-induced reductions in sleep disturbance may be another way that meditation helps improve mood disturbance. In the future, studies of mindfulness-meditation's effects on sleep should employ objective physiological measures of sleep such as comprehensive overnight polysomnographic recordings.

Imaging studies

In the last few years, imaging techniques have been applied to studying the effects of meditation on the brain. The types of meditation, subject populations, control conditions and imaging type all vary across studies without any systematic comparison, and therefore these studies should be regarded as largely exploratory. Nevertheless, these studies suggest that many of the areas of brain activation during meditation are the same brain areas that are dysfunctional or hypoactive in depression. For example, functional MRI (fMRI) data showed increased activation in dorsolateral prefrontal cortex, hippocampus/parrahippocampus, temporal lobe and the anterior cingulate (ACC) during the Relaxation Response in comparison to an active control condition in which subject

randomly generated a list of animals and did not observe their breathing (Lazar et al., 2000). Similarly, Single Photon Emission Computed Tomography (SPECT) data showed increased blood flow to the dorsolateral PFC, cingulate, and orbital frontal during meditation vs. an eyes-closed resting control condition in experienced Tibetan meditators (Newberg et al., 2001). Functional MRI studies of concentrative meditation and lovingkindness meditation vs. non-meditation condition both showed increased activation in the anterior cingulate, in both experienced and novice meditators, while increased frontal activation was found only in experienced meditators (Brefczynski-Lewis, Lutz, & Davidson, 2004; Lutz, Brefczynski-Lewis, & Davidson, 2004). Another study (Lou et al., 1999), which examined PET activations during multiple types of guided meditation found a consistent activation in both hippocampi in all forms of meditation, but deactivation in prefrontal and cingulate areas, compared to passive silent "non-meditation" control conditions. Given that many rest conditions show activation of the medial temporal lobe (i.e. hippocampus) compared to alternative baseline control conditions (Stark & Squire, 2001), these findings should be interpreted with caution, and future studies should pay closer attention to the type of control conditions used.

Insert table 3 about here

Conclusion

Mindfulness and other related forms of meditation are associated with improvement in depressive symptoms as well as with physiological changes that counteract those seen in depression (See Table 3 for a summary). Meditation is associated with decreases in the hyperactivation of a wide number of stress-related systems that is

associated with the progressive acceleration or "kindling" of depressive illness. For example, one of the most consistent effects of meditation is the normalization of the HPA axis and its multiple chemical tributaries, CRH, ACTH, cortisol, NE, 5-HT**,** proinflammatory cytokines, and DHEAS. Meditation increases activation in areas that are hypoactive in depression, such as the hippocampus, prefrontal cortex and anterior cingulate. Similarly, mindfulness may also reverse suppression of specific immunity that is related to right-sided brain activity, as well as the overproduction of pro-inflammatory cytokines that are associated with depression. Preliminary results suggest that 8 weeks of mindfulness training may shift a right-sided brain asymmetry like that associated with depression to a left-sided one that is associated with positive affect. A few studies of sleep and vagal tone suggest that these two indices of sympathetic/parasympathetic balance may be promising avenues of research as well. Meditation's ability to dampen or counteract these naturally escalating disturbances may help thwart the progressive course of depression and reduce the likelihood of future episodes.

Future Directions: Neuroplasticity

Overactive stress systems and the resulting poverty of neuromodulators and trophic factors like estrogen, 5-HT and BDNF are associated with a compromised neurogenic environment, resulting in a lack of new neurons in synapses and eventually atrophy in specific brain areas. Restoration of the neurogenic environment parallels improvement in depression. Neurogenesis and neuroplasticity are undoubtedly the most exciting direction for future research in meditation and depression. However, existing

studies have only been able to indirectly suggest evidence for meditation-related increases neurogenesis or plasticity.

One concrete idea for a more direct measurement of neuroplasticity and synaptogenesis involves an exciting new technology that has enabled researchers to use PET (positron emission tomography) to visualize 5-HT1a receptors in the brains of human subjects (e.g. Neumeister et al., 2004). A new radioactive tracer (FCWAY) binds to these receptors, revealing their locations and a numerical count by brain region. The resulting PET scans can be overlaid with structural MRI scan, so that the receptor sites can be precisely matched with brain structures. As mentioned previously, the 5-HT1a receptor, which mediates 5-HT-induced increases in neurogenesis, is markedly reduced in patients with depression and/or anxiety disorders (Drevets et al., 1999; Neumeister et al., 2004). Specifically, the receptor is lacking in the anterior and posterior cingulate, both of which have been implication in anxiety and depressive disorders (e.g. Charney & Drevets, 2002), and in the raphe nucleus in the midbrain, where 5-HT is synthesized and released. To the extent that meditation training regulates the 5-HT system, and positively affects the expression of 5-HT receptors, including 5-HT1a, it would be interesting to investigate the levels of the receptor pre and post an 8-week course in mindfulness meditation. In addition to providing the most direct evidence of neuroplasticity, this type of study would also sidestep the problems with measuring neurotransmitter levels via metabolites in blood, urine or saliva.

Given that many of the physiological abnormalities found in depression persist into remission and increase risk of relapse, the ability of meditation to reverse these

changes would provide an important mechanism of meditation-based relapse prevention. Unfortunately, the lack of research on the physiological effects of meditation far outweighs the available research. To date, no studies employing objective measures of meditation effects on sleep disturbance, synaptogenesis or neurogenesis have been published. Furthermore, very few of the studies that do exist are specific to a systematic method of mindfulness training with an adequate control group. While many more physiological studies of mindfulness are needed to develop a physiolological model of mindfulness and depression, the results of studies with other forms of meditation provide promising avenues of investigation.

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Tables

Table 1

Stress-related substances and their role in depression and neurogenesis

Associated with Depression	Exert Antidepressant effects
↑ inflammatory cytokines	↓ inflammatory cytokines cytokines
↑ cortisol	↓ cortisol
↓ serotonin	↑ serotonin
↓ estrogen	↑ estrogen
↓ BDNF	↑ BDNF
↓	↓
↓Neurogenesis	↑Neurogenesis

Table 2

1st author	year	N	sample	design/control	meditation	scale	Pre M(SD)	Post M(SD)	Follow-up	Pre-post reduction	ES
Astin	2003	128	FMS	RCT- vs. educ/Support vs. 3	MM/Qiqong	BDI	†16.7(7.4)	13.1(.1)	12.1(7.6)[e]	22%**	
Bedard	2003	13	TBI	dropouts	MBSR	BDI-2	†18.4(12.2)	9.7 (10.6)		47%*	0.31
Kabat-Zinn	1992	22	Anxiety-panic	SG-RM	MBSR	HRSD	†31.1(8.4)	23.7 (5.6)	25.1(7.0)[d]	24%**	
						BDI	†16.5(10.9)	10 (9.6)	7.5 (8.8) [d]	39%**	
Kristeller	1999	18	binge eating	SG-EBL	MBSR	BDI	†17.5(12)	9.11(6.9)		48%***	
Waelde	2004	14	caregivers	SG-RM	Med-yoga	CES-D	†23.5(17.8)	18.6(17.1)		21%**	1.02[a]
Speca	2000	109	cancer	RCT-WLC	MBSR	POMS-d	†14.1(10.5)	8.4((8.9)		40%**	
Klein	1985	74	depression	RCT- therapy + running	Med-yoga	SCL90-d	†2.6(0.7)	0.83(0.5)		68%*	0.98
Sagula	2004	39	chronic pain	vs. pain clinic TAU	MBSR	BDI-short	†9(6.5)	4.6 (3.9)		49%*	
Reibel	2001	136	Medical pts	SG-RM	MBSR	SCL-90 d	†1.0(.72)[b]	0.67(.72) [b]	0.66(.1) [f]	34%***	.47
Shepard	1997	44	corporate	vs. stress mgt	TM	IPAT-D	§52.8(30.8)	34.6(27.2)	30.9(30.8)[g]	34%*	
Gross	2004	20	transplant	SG-RM	MBSR	CES-D	13.0(11.1)	7.5(6.9)	10.4(7.6) [d]	42%*	0.72[a]
Kabat-Zinn	1985	90	Chronic pain	vs. Pain clinic TAU	MBSR	POMS-tmd	§47.8(na)	21.5(na)		55%*	
Tloczynski	1998	75	undergrad	RCT-Relax + education	Zen Breath	CAS-d	§23.4[c]	21.0 [c]		10%*	
Shapiro	1998	78	Med student	RCT-WLC	MBSR	SCL-90d	.87 [c]	.57 [c]		34%*	
Surawy	2005	18	CFS	RCT-WLC	MBSR/CT	HADS	§9 (4.5)	8.33(3.8)		7% ns	
Smith	1995	36	undergrad	RCT- HP + control	RR "peace"	BDI	§-9.6 from baseline			___-*	1.02

Note: Sample (TBI, traumatic brain injury; FMS, fibromyalgia; CFS, chronic fatigue syndrome)
Design/control (RCT, randomized controlled trial; WLC waitlist control; SGRM, single group repeated measures SGEBL, single group extended baseline; TAU treatment as usual)
Scale (SCL-90-d Depression subscale of Hopkins Symptom Checklist; POMS-d or -tmd, Depression subscale/total mood disturbance scale of the Profile of Mood States; CES-D Center for Epidemiological Studies Depression Scale; HRSD, Hamilton Rating Scale for Depression; IPAT-D, Institute for Personality and Ability Testing; CAS-d, College Adjustment Scale; HADS, Hospital Anxiety and Depression-Scale)
ES, reported effect size
[a] refers effect size calculated for single group repeated measures
[b] indicates averaged standard deviation of pre and post treatment scores
[c] indicates approximate means derived from figures
[d] 3 month follow-up
[e] 6 month follow-up
[f] 1 year follow-up
[g] 3 year follow-up

†Denotes clinically significant levels of depression as defined by a BDI and CES-D scores >16, BDI-2>14, HRSD>17, BDI-short form/POMS-d>7 and SCl-90-d >1.0. See Beck & Beck (1972) Dozois & Dobson (2002), Mulder (2000) and Wilkins et al (1995).
§Clinically significant cutoff score not established, or baseline scores not available

*p<.05, **p<.01, ***p<.001 for pre-post reduction

Table 3

Reversal of Depression-related Abnormality by Meditation

Depression-related abnormality	Reversal through meditation	
	MBSR/MBCT	TM/RR/other
R>L Frontal Asymmetry	Davidson, 2003	
↓ PFC activation		Lazar, 2000 ; Newberg, 2001; Lutz, 2004; Lazar, 2004
↓ ACC activation		Lazar, 2000 ; Newberg, 2001; Brefczynski-Lewis, 2004; Lutz, 2004
↓ hippocampal activation		Lazar, 2000; Lou, 1999
Low vagal tone		Travis, 1999
Elevated cortisol levels	Marcus, 2003; Carlson, 2004	Maclean, 1994; Kamei, 2000 ; Sudsuang, 1991; Walton, 1995
Abnormal cortisol profiles		
Catecholamine disturbance		Infante, 2002 ; Lang, 1979; Walton, 1995; Bujatti, 1976; Benson, 1983; Mills, 1990
Serotonin depletion		Bujatti, 1976; Loliger, 1991; Walton, 1995; Solberg, 2004
Elevated ACTH		Infante, 1998
Memory disturbance	Williams, 2000	Brasted, 2003
↓ Specific immunity	Davidson, 2003; Robinson, 2003	
Acute phase cytokine elevation	Carlson, 2003	

executive dysfunction	Valentine & Sweet, 1999	Linden, 1973; Pelletier, 1974; Brasted, 2003; Chan, 2004
Sleep disturbance	Shapiro, 2003; Carlson,2003;2004;2005; Gross, 2004; Singh, 1998; Heidenreich, 2004; Bootzin, 2005; Britton, 2005	Cohen, 1998
Increased cell loss/ Decreased neurogenesis	Lazar, 2005	
Decreased NO		Dusek, 2005

Note. Only first authors and dates are displayed. For full citation, refer to text.

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APPENDIX B: ELECTROENCEPHALOGRAPHIC SLEEP PROFILES BEFORE AND AFTER MINDFULNESS-BASED COGNITIVE THERAPY IN PARTIALLY REMITTED DEPRESSION

Electroencephalographic sleep profiles before and after Mindfulness-Based Cognitive Therapy in partially remitted depression

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Abstract

Study Objectives: Previous studies have indicated that mindfulness and other forms of meditation training are associated with improvements in sleep quality. However, none of these studies used objective polysomnographic sleep recordings. The aim of this study was to examine whether mindfulness meditation was associated with improvements in objectively measured sleep, according to polysomnography (PSG), and to relate changes in PSG sleep to subjectively reported changes in sleep and depression.

Design: Randomized waitlist control trial

Setting and Participants: 52 individuals with partially-remitted unipolar recurrent depression, ages 18-65. Approximately 50% of the sample was taking antidepressant medications.

Interventions: Mindfulness-Based Cognitive Therapy (MBCT), an 8-week manualized intervention with a central focus on the practice of mindfulness meditation techniques.

Measurements and Results: According to PSG, MBCT was associated with several indices of increased arousal, including less slow-wave sleep, increased arousals, awakenings and stage 1 sleep, relative to controls. An interaction with antidepressant medication use found that arousals, awakenings and stage 1 decreased in the medicated MBCT group. REM sleep changes were minimal. According to sleep diaries, wake after sleep onset (WASO) decreased more in the MBCT group than controls ($p<.05$). Beck Depression Inventory scores decreased more in the MBCT group than controls ($p<.01$). Improvements in depression were associated with duration of meditation practice, increased subjective sleep continuity, and increased PSG arousals.

Conclusions: Mindfulness meditation is associated with increases in objectively measured arousal during sleep with simultaneous improvements in subjectively reported sleep quality and mood disturbance. This pattern is similar to the profiles of positive responders to common antidepressant medications.

Key Words: Mindfulness-based cognitive therapy, meditation, sleep, arousal, depression

Introduction

A number of studies have reported improved sleep quality following mindfulness or meditation training using subjective measures such as self-report questionnaires and sleep diaries,[1-5] or objective measures such as actigraphy.[6] No longitudinal meditation studies have used overnight polysomnographic (PSG) recordings, the objective "gold standard" in sleep research, to assess the effects of meditation training on sleep in sleep-disturbed populations.

The purpose of the current study was to replicate the previous findings with objective polysomnographic measurement of sleep in a sample of individuals with partially remitted depression. This investigation was part of a larger study that explored the potential neurophysiological systems involved in mindfulness meditation's effects on recurrence in depression.

Sleep continuity disturbances are concomitant, prodromal and residual symptoms of major depression, and can be manifested by increased sleep onset latency (initiation insomnia), increased awakenings, arousals, or wake after sleep onset (maintenance insomnia), as well as by increased light sleep (stage 1) and less deep sleep (slow-wave sleep, NREM stages 3 and 4). In addition to the common complaint of insomnia or non-restorative sleep, about 40% of depressed outpatients exhibit signs of REM sleep disinhibition,[7] as manifested by early onset REM sleep,[8] increased REM sleep duration in the first cycle,[9] and increased REM density.[10] For recent reviews of sleep and depression, see Benca, Obermeyer, Thisted, and Gillin,[9] Reimann, Berger, and Vodenholzer.[11]

Psychosocial and pharmacological interventions for depression have differential effects on electroencephalographic sleep profiles. The most common antidepressants medications, serotonin-reuptake inhibitors (SSRIs), norepinephrine-reuptake inhibitors (NRIs), tend to increase nocturnal awakenings, although successfully-treated patients complain of less insomnia.[12] Most antidepressants (SSRIs, TCAs and MAOIs) delay REM onset, and decrease REM density and REM duration, which led to the theory that REM suppression was a central mechanism of antidepressant action.[11, 13] However, newer antidepressants with mechanisms of action that include 5-HT_2 receptor antagonism (nefazadone, mirtazepine) or dopamine reuptake blockade (bupropion) have been found to increase REM sleep and to have no effect on or even decrease REM latency,[14-16] which poses new questions about the role of REM sleep in depression.

In contrast to pharmacotherapy which produces paradoxical findings in objective and subjective measures, psychosocial interventions, such as Interpersonal Therapy (IPT) and Cognitive Behavioral therapy (CBT), are associated with improvements in PSG sleep continuity that correspond with subjective reports. Psychosocial interventions do not tend to have the strong REM suppressing effects as pharmacotherapy, although small reductions in the frequency of eye movements (REM density) have been reported.[17-20]

Sleep disturbances, in earlier episodes, often coincide with or precipitate depressive symptomatology and subside upon remission.[12] However, there is evidence that these abnormalities may become less depression-dependent as episodes progress. That is, these disturbances may continue to linger despite clinical improvement and are associated with residual symptoms and increased risk for relapse. Therefore, the

treatment of residual sleep abnormalities during partial remission in individuals with a chronic history of depression may be an important step in preventing relapse and recurrence.

In the present study, we investigated the effects of an 8-week course of Mindfulness-Based Cognitive Therapy on electroencephalographic sleep profiles in individuals with partially remitted chronic depression. Based on previous reports of improved sleep quality following meditation, we predicted that MBCT would 1) improve sleep continuity, as manifested by a decrease in a) sleep onset latency (SOL), b) awakenings, c) arousals d) wake after sleep onset (WASO), and e) an increase in sleep efficiency; and 2) deepen sleep, as manifested by a) decreased stage 1 sleep and b) increased slow-wave sleep.

Because this is the first longitudinal meditation study to use polysomnography, the effect of MBCT on REM sleep is unknown. If MBCT is similar to CBT, we would predict no change in REM latency or REM duration. Because MBCT incorporates a more somatically-based component (i.e. meditation) with known associations to increases in monoamine neurotransmitters,[21-24] MBCT may act similarly to antidepressant medications. In this case, we would predict an increased REM latency and decreased REM duration in participants that are not already taking antidepressants. We did not predict REM sleep modifications in medicated subjects since REM is strongly suppressed by antidepressants.

In order to more closely investigate the potential relationship between sleep and meditation, we used minutes of daily meditation practice as well as group assignment in

our analyses. In order to imbed the findings within the context of clinical utility, we ran follow-up analyses to examine the relationships between treatment assignment, meditation practice minutes, sleep changes and Beck Depression Inventory scores.

Method

Participants:

Participants were recruited through community advertisements. Participants (n=52) were 75% female with a mean age of 47.4 years (range=24-64 years). A structured clinical interview for Axis I (SCID-I) and Axis II (SCID-II) disorders, the Beck Depression Inventory and the Hamilton Rating Scale for Depression (HRSD-24) were administered to determine current diagnostic status. Participants met DSM-IV criteria for major depression within the last 60 months, but not the last 8 weeks, and they had a score of 20 or less on the HRSD-24. If they were taking antidepressant medication (AD), they reported no change in medication type or dose for 3 months prior to enrollment, or during the active phase of the study.

Participants were excluded if a) they had a history of bipolar disorder, cyclothymia, schizophrenia, schizoaffective disorder, persistent antisocial behavior or repeated self-harm, borderline personality disorder, organic brain damage, b) current panic, obsessive-compulsive disorder, eating disorder, or substance abuse/dependence, c) they could not read and write in English, d) they were receiving current psychotherapy or e) they already had a regular meditation practice. Participants were also excluded if they had or suspected an untreated sleep disorder besides insomnia. Two participants with suspected sleep disorders underwent independent polysomnographic screenings with

negative results and were allowed to enroll. The study protocol was approved by the University of Arizona institution review board, and all participants provided written informed consent for research participation.

Design:

Participants completed 3 weeks of sleep diaries and pre-treatment questionnaires before baseline assessments in the laboratory. After completion of the adaptation night and baseline assessment in the sleep laboratory, a block randomization procedure was used to assign each block of 5 participants to the MBCT program or waitlist control condition in a 3:2 ratio. After 8 weeks of treatment or waitlist condition, participants completed a post-treatment questionnaire packet and returned to the laboratory to repeat the study-night procedure (no post-treatment adaptation night). Participants also completed sleep daily diaries for the duration of the treatment condition. Waitlisted subjects entered the next available wave of the MBCT program, after completing the 2nd assessment. See Figure 1 for an overview of the study design.

<insert figure 1 about here>

Pre- and post- treatment assessments:

Participants underwent an adaptation night in the sleep laboratory and returned within 1 week for a "study night." Participants were asked to abstain from alcohol, caffeine and other substances that may interfere with sleep for 24 hours before the study. In addition, they were asked to refrain from vigorous exercise within 2 hours of arrival to the study night, to avoid scheduling either appointment after an anticipated stressor (like an exam, etc.), and not to alter their regular sleep schedule or take naps the day of the study.

Polysomnography/EEG. In the sleep laboratory, scalp electrodes were applied according to the International 10-20 system at all 19 standard placements as well as reference electrodes placed between Cz and Pz and at the mastoids, A1 and A2. Eye movements (Electrooculogram or EOG) were recorded with electrodes placed at the lower left outer canthus (LOG), and upper right outer canthus (ROG). Muscle activity (electromyogram or EMG) was recorded with three electrodes placed on the mentalis and submentalis muscles of the chin. Maximal electrical impedance at bedtime was set at 5 K Ohms. All scalp electrodes were referred to a reference electrode that made alternative montages possible offline. All physiological measurements were recorded into the 32-channel AC amplifier system of a Grass Polysomnograph, Aurora Model and Twin 3.2 Software (Grass Instrument Division, Astro-Med, Inc., West Warwick, RI). After biological calibrations, participants were allowed to read until they asked for lights out. Each subject was allowed to sleep for 9 hours after the first epoch of sleep, and was continuously monitored by video camera.

Sleep Parameters: Each record was scored in 30 second epochs according to Rechtschaffen and Kales (1968) standard sleep stage scoring guidelines. Arousals were visually scored according to American Sleep Disorders Association (ASDA) scoring rules.[25] Records were scored by a registered polysomnographic sleep technician (RPSGT) who had an interrater reliability of >.90 with other RPSGTs, and who had no knowledge of diagnostic status, treatment group or phase of treatment. Sleep stages were calculated into minutes and percentage (of total sleep time) of each stage and a number of other sleep parameters. Sleep onset was defined by the first epoch of any stage of sleep. Sleep

onset latency (SOL) refers to the time between lights out and sleep onset. Sleep efficiency (SE) is the ratio of total sleep time (TST) to total record time from lights out until the final awakening.

Depression: The Hamilton Rating Scale for Depression (HRSD-24) is a widely used clinician administered interview assessment of depressive symptomatology. A modified 31-item version[26] was used, although reported HRSD scores are based on the standard 24-item version. Interviewers established an interrater reliability >.90 with other raters of the same HRSD version. The Beck Depression Inventory (BDI)[27] is a 21-item self report measure that assesses depressive symptomatology, with an emphasis on cognitive symptoms. Sleep-related items on the BDI were omitted for correlations with sleep variables, but otherwise were retained in order to convey overall clinical significance.

Sleep Diaries: Participants kept track of their sleep for a 3 week baseline, and for the 9 weeks of the treatment phase. Each morning the participant recorded a) the number of hours slept (Total sleep time, TST), b) the time spent in bed (Time in bed, TIB), c) sleep onset latency (SOL) , d) number of awakenings (NWAK), e) number of minutes awake at each awakening, f) the type and dose of any sleep-related medications, g) and minutes of napping. The diary data were then used to calculate sleep efficiency, and wake after sleep onset (WASO; number of awakenings x minutes of each awakening).

Meditation logs: Participants in the MBCT group kept track of their daily meditation practice during the 8 weeks of active treatment. Diaries included information about formal meditation practice including: a) the type of meditation (body scan, breath awareness etc.), b) the number of minutes practiced, c) the time of day practiced and d)

whether they fell asleep during practice; and informal practice (walking, mindful activities).

Treatment

Mindfulness-Based Cognitive Therapy (MBCT) is an 8-week group intervention with psychoeducational and client-centered format.[28] Participants attended weekly 3-hour sessions and an all-day silent retreat during the 6th week for a total of 9 sessions. Sessions focused on cultivating mindfulness or non-judgmental present-moment awareness of mental content and everyday activities, including sitting, lying down, breathing, walking, and other simple movements. Homework assignments consisted of practicing mindfulness meditation exercises with the aid of a guided audio tape and completing worksheets related to stress, automatic thoughts, and common reactions to various types of events. Improving sleep quality was not an explicit goal of treatment. A session-by session description with handouts and homework assignments is available in the MBCT manual.[28] Sessions were instructed by the first author (W.B.) who has received extensive training in delivery of the program through the Center for Mindfulness Mindfulness-Based Stress Reduction Instructor Certification Program at University of Massachusetts Medical School, and through MBCT training with Dr. Zindel Segal, the first author of the MBCT manual. Sessions were supervised by two licensed clinical psychologists.

Data Analysis

Preliminary analyses were used to investigate baseline characteristics, severity of sleep disturbance and any baseline group differences that might affect the main analyses.

Main Analyses investigated the effect of treatment on sleep quality according to two different methods of data collection: overnight polysomnographic recordings (objective laboratory measurement) and sleep diaries (subjective reports). In the main analyses, we conducted separate 3-way repeated measures MANOVAs to examine changes in PSG and diary sleep variables from baseline to post treatment. PSG sleep variables were two-level within subject variables (pre, post) variables and consisted of Total Sleep Time (TST), sleep efficiency (SE), arousals, awakenings, sleep onset latency (SOL), stage 1 minutes, SWS minutes, REM minutes (first cycle only and total), and REM latency. Diary sleep variables consisted of TST, SE, awakenings, SOL, and naps. Between subjects variables were treatment (MBCT, control) and antidepressant medication status (1=meds, 0=no meds), because antidepressant status had numerous effects on sleep architecture at baseline. Significant 3-way interactions were decomposed with separate repeated measures MANOVAS according to Maxwell and Delaney.[29] Specifically, in the presence of a significant 3-way interaction, separate treatment x time ANOVAs were conducted at each level of medication status. Effects of AD medication on sleep were only reported for baseline differences in the preliminary analyses, and then only in the context of medication x treatment interactions in the main analyses. Because of the exploratory nature of the study and the relatively small sample size, all trends ($p<.10$) that related to main predictions were reported in order to identify patterns in data that warrant future investigation. Effect sizes were reported as partial η^2.

Follow-up analyses used Pearson product moment correlation coefficients to examine the relationships between the amount of meditation practice, changes in PSG and diary sleep and changes in depression scores.

Results

Preliminary Analyses:

Participants/Attrition: Fifty-two individuals completed baseline assessment and randomization procedures (29 MBCT, 23 controls) and 7 dropped out once enrolled (2 MBCT, 5 controls), so that a total of 45 completed all assessments (27 MBCT, 18 controls). Of the completers, 93% completed diaries for all 8 weeks.

Treatment Attendance and Adherence: Out of the 29 MBCT participants, 2 dropped out after the 2nd class. Of the remaining 27, 26 (96.3%) attended at least 8 of the 9 sessions, and one person attended 7 sessions. Outside of class, the 27 completers engaged in formal meditation practice an average of 39.9±10 minutes/day, 5.2±1.2 days/week. According to the goal of 45 minutes, 6 days/week of formal meditation practice (270 minutes/week=100%), the mean adherence across all weeks was 76±24%.

Baseline characteristics: Participants (n=52) were 75% female with a mean age of 47.4 years (range=24-64 years). Months of previous depression ranged from 11-180, mean 60.5±38.2 months. Approximately half of the participants in each group were in remission (as defined by a BDI score<10) and about half were taking antidepressant medications (48.3% MBCT; 52.2% controls). There were no significant differences between treatment groups in age, gender, current depression level, duration of previous depression, the frequency or type of antidepressant (SSRI, NRI etc.) or any other

medication, or any baseline objective sleep measure. See table 1 for summary by treatment group.

<Insert table 1 about here>

Baseline sleep disturbance: According to sleep diaries, 33.3 % of the sample met severity and frequency criteria for insomnia, defined as ≥ 31 minutes of WASO or SOL on ≥ 3 nights/week during the first week of baseline assessment.[30] Sixty percent of the sample had average baseline sleep efficiencies less than 85%, a common cut-off for distinguishing good sleepers from those with insomnia.[31] According to PSG, 42.3% had sleep efficiencies below 85% (although 70% had PSG sleep efficiencies of less than 90%), 65% had WASO ≥ 31 minutes, and only 7.7% had SOLs as ≥ 31 minutes.

Because REM sleep is known to be strongly suppressed by antidepressant medications, REM sleep indices were analyzed separately by medication status. Within the non-medicated group, 38.5% had pathologically short REM latencies, defined as <65 minutes,[17, 32] while 77% had latencies of 80 minutes or less. In the medicated group, 23.1% had REM latencies less than 65 minutes, and 38.5% less than 80 minutes. Half of the medicated group had REM latencies >100 minutes and 20% over 200 minutes.

Reduced slow-wave sleep, as defined by less than 8% of total sleep time,[17] was apparent in 80% of the sample, with no difference between medicated and non-medicated participants. See table 2 for all objective sleep variable means in each group.

<Insert table 2 about here>

Medication and Depression Status effects: Remission status had minimal effects on sleep quality, affecting only total sleep time. Remitted participants slept longer than non-

remitted, t(43.9)=-2.47, p=.018. Antidepressant medication, however, had a dramatic effect on sleep quality and microarchitecture. Medicated individuals had more disturbed sleep, as manifested by more arousals, t(50)=3.0, p=.005, and minutes of stage 1, t(45.3)=2.52, p<.02. Medicated individuals also had shorter REM latencies, t(28)=3.2, p=.003), and less REM as a percent of total sleep time, t(50)=-2.6, p=.013.

Main Analyses: PSG Data

Two individuals were excluded from the sleep analysis at time 2, due to illness and incorrect circadian scheduling which resulted in less than 30% of their typical sleep time.

No time main effects or treatment x time interaction effects emerged for any objective sleep continuity measure. Significant 3-way (treatment x time x AD medication status) interactions were found for arousals F(1,39)=4.74, p=.04, ES (effect size, partial η^2): =.11, awakenings, F(1,39) =9.5, p=.004, ES=.20 and number of stage 1 minutes F(1,39)= 8.52, p=.006, ES=.18.

First, we examined the effect of time x condition at each level of medication status. In the non-medicated subjects, MBCT showed trends toward greater increase in arousals, F(1,18)=2.43, p=.14, ES=.10, awakenings, F(1,18)=4.5, p=.05, ES=.19 and stage 1 minutes, F(1,18)=3.29, p= .087, ES=.15 than controls. In medicated subjects, the MBCT group showed greater decreases in arousals, F(1,21)=2.2, p=.15, ES=.12, awakenings, F(1,21)=4.90, p=.04, ES=.19 and stage 1 minutes F(1, 21)=5.59, p=.03, ES=.21 than controls.

<insert figure 2 about here>

Slow-wave sleep**:** A significant main effect of time on minutes of slow-wave sleep indicated general increase in SWS from –pre to –post treatment for all patients, F(1,39)=10.78, p=.002, ES=.22. There was also a significant 2-way (treatment x time) interaction . Controls showed a significantly larger increase in SWS minutes than the MBCT group, F(1,39)=5.94, p=.02, ES=.13. No 3-way interaction emerged.

<insert figure 3 about here>

REM sleep: No time main effects or treatment x time interaction effects emerged for REM sleep duration. There was a significant 3-way (treatment x time x AD) interaction for total number of minutes of REM sleep. In medicated subjects, there was a trend toward a greater increase in REM minutes in the MBCT group, F(1,21)=3.34, p=.08, ES=.14. The non-medicated MBCT group and medicated controls showed a non-significant decrease in REM minutes.

There were no significant main effects or interaction effects for treatment, time or medication on the duration of the first REM cycle. Because a priori hypotheses predicted REM changes in the non-medicated MBCT group only, we ran t-tests for that group alone. The non-medicated MBCT group decreased (M_{diff}=-2.61 min) relative to the non-medicated controls (M_{diff} =+3.57 min), but the difference was not statistically significant.

There were no significant main effects or interaction effects for group, time or medication status on REM latency. Mean REM latency increased nonsignificantly in the non-medicated MBCT group (M_{diff}=6.57 minutes, p=ns) and decreased in all other groups (see table 2).

Main Analyses: Sleep diaries

There were significant main effects for time indicating increased sleep efficiency, F(1, 38)=18.50, p=.0001, ES=.33, decreased WASO, F(1,38)=8.96, p=.005, ES=.19, decreased awakenings F(1,38)=13.61, p=.001, ES=.26, and decreased sleep onset latency, F(1,38)=13.90, p=.0006, ES=.27 across all subjects. There was a significantly greater decrease in WASO in the MBCT group vs. controls, F(1,38)=4.57, p=.05, ES=.19, although all other treatment x time interactions were non-significant. There was a significant 3-way (treatment x time x AD) interaction for sleep onset latency F(1,38)=4.08, p=.05, ES=.10. There was a trend toward a greater decrease in SOL in non-medicated controls compared to the non-medicated MBCT group F(1,18)=4.19, p=.06. No statistically significant 3-way interactions emerged for sleep efficiency, WASO, or number of awakenings.

<Insert figure 4 about here>

Depression Scores:

There was a significant 2-way (treatment x time) interaction for Beck Depression scores, in which the treatment group showed a larger decrease than controls over time, F(1,43)=9.3, p=.004, ES=.18. No significant 3-way interaction emerged for depression scores.

<insert figure 5 about here>

Follow-up Analyses: Relationships between meditation practice, sleep and depression scores:

With both treatment groups combined (n=45), minutes of formal meditation practice per week were negatively correlated with changes in SWS percent (r=-.35,

p=.02), subjective WASO (r=-.35, p=.03), and BDI scores (r=-.35, p=.03), and positively correlated with increases in objective sleep efficiency (r=.31, p=.04). Within the MBCT group, formal meditation practice was positively correlated with improvements in objective sleep efficiency (r=.41, p=.04) and a decrease in both subjective time in bed (r=-.44, p=.03) and total sleep time (r=-.48, p=.02). Minutes of formal practice per week were positively correlated with combined PSG awakenings and arousals in the non-medicated MBCT group (r=.64, p=.02) and negatively correlated with PSG awakenings/arousals in the medicated MBCT group (r=.44 p=.16).

<insert figure 6 here>

With all groups combined, changes in BDI scores (with sleep-related items removed) were negatively correlated with changes in subjective sleep efficiency (r=-.56, p=.0005) and positively correlated with changes in subjective WASO, r=.48, p<.005. However, changes in BDI scores were negatively correlated with changes in PSG awakenings (r=-.31, p=.05), so that improvements in depression scores were associated with increases in objectively measured awakenings. Similarly, within the MBCT group, improvements in depression scores were marginally correlated with increases in stage 1 percent (r=-.40, p=.056).

Discussion

According to sleep diaries, MBCT effects on sleep replicated previous findings: MBCT was associated with improvements in a number of subjectively-reported sleep continuity indices, with a greater reduction in WASO than waitlisted controls. The data from the objective polysomnographic sleep recordings, however, tell a different story:

Contrary to previous research and predictions that mindfulness meditation would improve or deepen objectively measured sleep, several findings from this study suggest that mindfulness has an arousing effect on sleep. First, the MBCT group as a whole exhibited a suppression of slow-wave sleep compared to controls. Second, antidepressant medication-free individuals in the mindfulness group showed a significantly greater increase in awakenings, arousals and stage 1 sleep from pre- to post-treatment than controls. Third, there was a significant negative correlation between the amount of meditation practice and the need for sleep, such that the more minutes of meditation per week, the less time spent in bed or sleeping.

SWS increased significantly in controls, which may be a result of continued acclimation to the laboratory environment. The MBCT group, regardless of medication status, failed to show the same large increase in slow-wave sleep, which suggests that mindfulness training has some generally arousing effects that are specific to the SWS generator.

There was also some evidence that suggested that meditation practice, especially at "higher doses," decreases the need for sleep. Formal meditation practice was negatively correlated with both (diary) total sleep time and time in bed. While there was no overall difference between treatment groups in the magnitude of decreased TIB, there was a trend toward a significant difference when controls were compared to meditators who practiced at least 75% of the total goal minutes. One possible explanation for this finding would be that the meditators are actually sleeping during meditation practice, and therefore need less sleep at night. However, the reported frequency of falling asleep

during meditation practice was actually positively correlated with changes in TIB (r=.41 p=.05), such that the more meditation snoozing (i.e., less meditation), the larger increase in TIB.

In the special case of individuals taking antidepressant medications, who had more disturbed sleep at baseline, mindfulness training had a strong sleep-promoting effect, as manifested by a greater decrease in the number of PSG arousals, awakenings and minutes of stage 1, as compared to medicated controls. Formal meditation practice was correlated with decreased PSG arousals in medicated individuals and increased arousals in the non-medicated ones, which further suggests that mindfulness has opposite effects on sleep depending on medication status. This sleep-promoting effect of MBCT in medicated individuals did not extend to increases in SWS or increased sleep time. Like non-medicated participants in the MBCT group, SWS was suppressed relative to controls and higher doses of meditation were associated with less need for sleep.

Our prediction of mindfulness-related REM suppression or increase in REM latency in non-medicated individuals was not strongly supported. In comparison to non-medicated controls, the non-medicated MBCT group showed a decrease in REM minutes, a decrease in the duration of the first REM cycle, and increased REM latency. However, none of these differences were statistically significant. It is possible that because participants were not selected on the basis of sleep disturbances that the degree of REM abnormality was not severe enough to detect a treatment-related change.

The MBCT group showed a greater reduction in depression scores than controls, regardless of medication status. Improvements in depression scores were correlated with

improvements in subjectively reported sleep efficiency and WASO, but also with increases in PSG awakenings, and within the MBCT group, increases in stage 1 sleep. This pattern of improved mood and reported sleep quality with a concomitant increase in objectively measured arousal is common to patients who respond to antidepressant medications [12, 33] which may suggest that mindfulness training may affect similar systems as antidepressant medications (i.e. monoamine neurotransmitters).

Supporting the idea of a monoaminergic mechanism, several studies have suggested that meditation is associated with increases in norepinephrine, serotonin and dopamine,[21-24] However, long-term practice has been found to be associated with a down-regulation of functional beta-adrenergic receptors[34] which results in a desensitization to the arousing effects of norepinephrine. It is possible that meditation-induced increases of monoamines in medicated individuals (who already have high levels of monoamines) might lead to a faster down regulation of receptors, and result in a desensitization to the sleep effects of norepinephrine, namely increased arousals and REM suppression. This might explain why arousals decreased and REM minutes increased in the medicated subjects following meditation training. In the non-medicated subjects, who ostensibly have low or normal levels of monoamines, the meditation-induced increase in monoamines would have similar effects on sleep as antidepressants, i.e. an increase in arousal and a varied level of REM suppression.

Despite the common assumption that meditation promotes relaxation and sleep, the arousing effects of certain kinds of meditation are well-known.[35] Cross-sectional studies of Transcendental Meditation have similarly found that meditation practice was

associated with greater arousal on nocturnal electroencephalographic profiles. Mason et al.[36] found significantly more stage 1 and less SWS minutes in both long-term and short-term meditators vs. non-meditating controls. Meditation practice (in particular TM) has been repeatedly found to induce acute (state) and long-lasting (trait) increases in alpha and theta power during wake (for a review, see [37]) that also persist into nocturnal sleep, including slow-wave sleep.[36] While alpha-theta frequencies are considered "slow" compared to usual waking frequencies, and are associated with relaxation or drowsiness, the same frequencies represent increased mental arousal or alertness when they appear in sleep. Thus, the neurophysiological changes that accompany a deliberately cultivated mental state during waking may persist and alter the microarchitecture of sleep.

What are the clinical implications of meditation-related increases in neurophysiological arousal during sleep? At least in this case, meditation-related arousal in objective sleep was associated with improvements in depression. This finding is consistent with the antidepressant literature and with findings that sleep may be depressogenic[38] and that sleep deprivation has antidepressant effects[39]. This finding is also consistent with findings that meditation practice increases dopamine[24] and that dopamine release is associated with the antidepressant effects of sleep deprivation.[39]

The present study has several limitations, most notably the lack of statistical power due to small sample size and the relatively large number of analyses conducted. The use of a partially remitted depression sample limits the ability to generalize to more depressed samples or other clinical or non-clinical populations. The use of an 8-week mindfulness course limits the ability to speculate on the effects of other forms of

meditation or the effects of longer durations of training. Varying levels of mood and sleep disturbance at baseline may have diluted the effects of treatment, and future attempts should be made to select participants on the homogeneity of baseline characteristics targeted for treatment. The paradoxical effect of antidepressant medications, in particular, warrants further investigation, and should be paired with serum monoamine assays. Future studies should also employ multiple PSGs before, during and after training, as well as at several follow-up timepoints in order to increase reliability, investigate the timecourse of effects, and establish the clinical significance in regard to relapse and recurrence rates.

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Tables and Figures

Table 1

Baseline Characteristics by treatment group

	MBCT	SD	CON	SD
N	29		23	
% female	82.8		65.2	
Age	47.0	7.5	47.8	10.9
BDI	9.1	5.8	9.8	6.1
HRSD-24	10.4	6.1	13.2	6.6
dep months	59.6	38.2	61.7	39.1
% in remission	48.3		47.8	
% on AD	48.3		50.0	
% completers	93.1		78.3	

Note: BDI= Beck Depression Inventory; HRSD-24= Hamilton Rating Scale for Depression (24-item version); dep months= total number of months of previous depression across all episodes; remission=BDI score<10; AD=antidepressant medication

Table 2

Polysomnographic Sleep Data

		Baseline		Post-Treatment		MANOVA Fs	
Variable	treatment	mean	SD	mean	SD	F^1	F^2
N	MBCT-nad	13		13			
	CON-nad	7		7			
	MBCT-ad	12		12			
	CON-ad	11		11			
TST	MBCT-nad	365.5	85.5	383.9	51.9		
	CON-nad	354.9	57.5	397.2	54.6		
	MBCT-ad	387.4	41.2	381.5	81.8		
	CON-ad	413.5	67.3	390.5	75.4		
SE	MBCT-nad	83.5	13.7	85.5	5.0		
	CON-nad	87.5	5.7	88.4	6.7		
	MBCT-ad	85.2	5.1	87.3	7.7		
	CON-ad	87.0	8.7	82.6	13.5		
SOL	MBCT-nad	13.5	13.1	11.3	9.2		
	CON-nad	9.4	8.2	4.6	3.2		
	MBCT-ad	11.2	12.1	6.7	8.0		
	CON-ad	16.0	13.4	20.7	30.5		
Arousals	MBCT-nad	68.7	27.6	94.8	37.5	4.7*	2.4^b
	CON-nad	107.7	80.3	93.4	38.6		
	MBCT-ad	135.3	38.4	95.0	46.0		2.2^b
	CON-ad	109.9	45.8	98.5	41.1		
WASO	MBCT-nad	51.8	38.3	52.8	22.5		
	CON-nad	35.8	20.2	37.4	18.3		
	MBCT-ad	47.8	15.8	44.7	31.4		
	CON-ad	39.3	31.8	47.5	30.0		
NWAK	MBCT-nad	21.2	11.4	34.5	16.6	9.5***	4.5^{*b}
	CON-nad	30.6	14.9	26.3	6.3		
	MBCT-ad	42.5^a	13.2	31.2	16.6		4.9^{*b}
	CON-ad	28.2	8.8	28.8	11.3		
stage 1 min	MBCT-nad	24.7	6.2	35.5	15.8	8.5**	$3.3^{\dagger b}$
	CON-nad	30.7	19.8	28.6	11.1		
	MBCT-ad	41.3	11.2	31.4	13.7		5.6^{*b}
	CON-ad	33.0	21.1	35.9	22.9		
stage 1 %	MBCT-nad	7.2	2.4	9.4	4.7		
	CON-nad	9.4	8.0	7.6	4.1		
	MBCT-ad	10.6	2.6	8.5	4.3		
	CON-ad	8.7	6.8	9.1	4.8		
stage 2 min	MBCT-nad	233.6	57.3	244.7	39.9		
	CON-nad	226.1	37.5	243.5	34.3		
	MBCT-ad	262.6	42.1	249.0	70.0		

	CON-ad	260.8	51.1	238.4	57.0		
stage 2 %	MBCT-nad	64.1	7.6	63.8	6.9		
	CON-nad	64.1	7.2	61.5	6.1		
	MBCT-ad	67.5	6.7	65.1	9.6		
	CON-ad	60.7	9.5	61.2	11.2		
SWS min	MBCT-nad	13.5	11.4	14.3	13.0		9.5**
	CON-nad	15.0	12.8	27.5	20.0		
	MBCT-ad	22.3	25.5	24.4	37.6		3.3†[b]
	CON-ad	22.5	25.3	29.8	26.2		
SWS %	MBCT-nad	4.2	4.0	3.8	3.5		
	CON-nad	4.0	3.2	6.5	4.6		
	MBCT-ad	6.2	7.9	6.2	9.2		
	CON-ad	5.1	5.3	7.0	7.0		
REM min	MBCT-nad	93.8	44.9	89.5	31.9	5.3*	
	CON-nad	80.6	38.4	97.6	32.1		
	MBCT-ad	61.3	23.7[a]	81.8	28.8		3.3†[b]
	CON-ad	97.4	43.6	86.3	34.4		
REM %	MBCT-nad	24.5	8.0	23.0	7.7		
	CON-nad	21.8	8.5	24.3	6.0		
	MBCT-ad	15.7	5.8 [a]	20.1	5.3		
	CON-ad	22.8	8.2	21.9	6.2		
REMLAT	MBCT-nad	73.3	28.5	80.4	32.1		
	CON-nad	80.2	25.2	76.3	27.7		
	MBCT-ad	148.2	120.8	139.6	72.6		
	CON-ad	107.3	58.0	104.5	48.9		
1st REM	MBCT-nad	18.5	12.8	15.9	9.9		
	CON-nad	20.0	8.0	23.6	10.5		
	MBCT-ad	19.9	21.3	24.6	19.2		
	CON-ad	23.8	20.0	24.0	15.1		

Note: MBCT= Mindfulness-Based Cognitive Therapy; CON= Waitlist control; nad= no antidepressant medication; ad=antidepressant medication. TST= total sleep time (minutes), SE=sleep efficiency (%), SOL= sleep onset latency, WASO= wake after sleep onset (minutes), NWAK= number of awakenings, SWS= slow-wave sleep; REMLAT= REM latency (minutes); 1st REM= duration of first REM period (minutes)
F^1= 3-way repeated measures ANOVA interaction (treatment x time x AD) factor
F^2= 2 way interaction (treatment x time)
[a]= significant baseline difference between treatment conditions at same level of medication
[b]= treatment x time interaction for each level of AD
*p<.05 **p<.01 ***p<.005 †p<.10

Table 3

Sleep Diary Data

	condition	Baseline		Post-treatment		MANOVA Fs	
variable	condition	mean	SD	mean	SD	F^1	F^2
N	MBCT-nad	13.0		13.0			
	CON-nad	7.0		7.0			
	MBCT-ad	12.0		12.0			
	CON-ad	10.0		10.0			
TIB	MBCT-nad	488.8	51.0	478.3	33.3		
	CON-nad	499.8	74.9	510.3	62.5		
	MBCT-ad	511.5	64.6	492.8	62.1		
	CON-ad	527.5	58.3	509.3	50.6		
TST	MBCT-nad	395.9	62.2	424.5	39.2		
	CON-nad	400.5	59.2	434.0	53.0		
	MBCT-ad	423.6	82.3	435.4	65.2		
	CON-ad	446.0	69.3	439.4	58.5		
SE	MBCT-nad	80.5	9.2	88.6	5.7		
	CON-nad	79.9	9.3	85.5	7.4		
	MBCT-ad	83.1	12.0	88.5	9.2		
	CON-ad	84.3	6.6	86.1	6.5		
SOL	MBCT-nad	15.3	5.7	9.8	4.8	4.0*	4.1† [b]
	CON-nad	24.6	16.2	8.2	3.8		
	MBCT-ad	18.5	20.4	12.0	9.9		
	CON-ad	19.1	10.1	17.8	8.0		
NWAK	MBCT-nad	1.9	0.9	1.0	1.0		
	CON-nad	1.8	0.9	1.2	1.0		
	MBCT-ad	1.5	1.0	0.9	0.9		
	CON-ad	2.3	2.2	1.5	0.9		
WASO	MBCT-nad	26.7	30.6	10.1	16.6		4.6*
	CON-nad	14.7	16.0	9.3	10.4		
	MBCT-ad	26.8	41.5	16.8	26.7		
	CON-ad	14.7	13.5	15.7	23.4		
naps (min)	MBCT-nad	4.5	9.2	9.1	11.2		
	CON-nad	15.3	14.6	6.9	10.6		
	MBCT-ad	9.8	12.6	9.3	10.9		
	CON-ad	7.7	16.5	11.4	8.2		

Note: MBCT= Mindfulness-Based Cognitive Therapy; CON= Waitlist control; nad= no antidepressant medication; ad=antidepressant medication. TST= total sleep time (minutes), SE=sleep efficiency (%), SOL= sleep onset latency (minutes), NWAK= number of awakenings, WASO=wake after sleep onset (minutes)

F^1= 3-way repeated measures ANOVA interaction (treatment x time x AD) factor

F^2= 2 way interaction (treatment x time)

[a]= significant baseline difference between treatment conditions at same level of medication

[b]= treatment x time interaction for each level of AD

*p<.05 **p<.01 ***p<.005 †p<.10

Figure legends

Figure 1: Study Design

Figure 2: Mean change (and standard error) in number of A) PSG awakenings, B) PSG arousals and C) stage 1 minutes for medicated and non-medicated subgroups within each treatment group (MBCT or waitlist control).

Figure 3: Mean change (and standard error) in number of PSG slow-wave sleep minutes for medicated and non-medicated subgroups within each treatment group (MBCT or waitlist control).

Figure 4: Mean change (and standard error) in number of diary wake-after sleep onset (WASO) minutes for medicated and non-medicated subgroups within each treatment group (MBCT or waitlist control).

Figure 5: Mean change (and standard error) in Beck Depression Inventory (BDI) scores for medicated and non-medicated subgroups within each treatment group (MBCT or waitlist control).

Figure 6: Correlation between changes in combined number of arousals and awakenings and mean number of minutes of formal meditation per week (in MBCT group only).

Figure 1

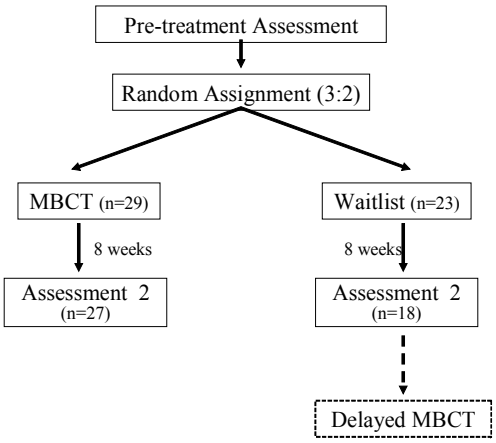

Pre-treatment Assessment
Random Assignment (3:2)
MBCT (n=29)
Waitlist (n=23)
8 weeks
8 weeks
Assessment 2
(n=27)
Assessment 2
(n=18)
Delayed MBCT

Figure 2

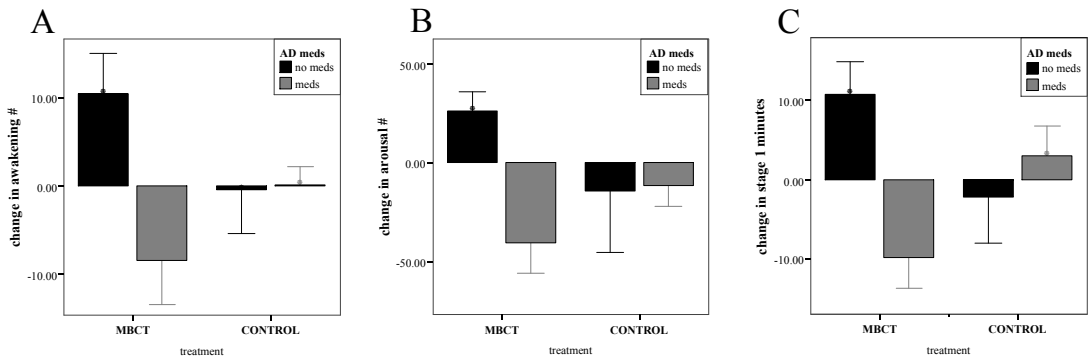

A
AD meds
no meds
meds
change in awakening #
10.00
0.00
-10.00
MBCT
CONTROL
treatment
B
AD meds
no meds
meds
change in arousal #
50.00
0.00
-50.00
MBCT
CONTROL
treatment
C
AD meds
no meds
meds
change in stage 1 minutes
10.00
0.00
-10.00
MBCT
CONTROL
treatment

Figure 3

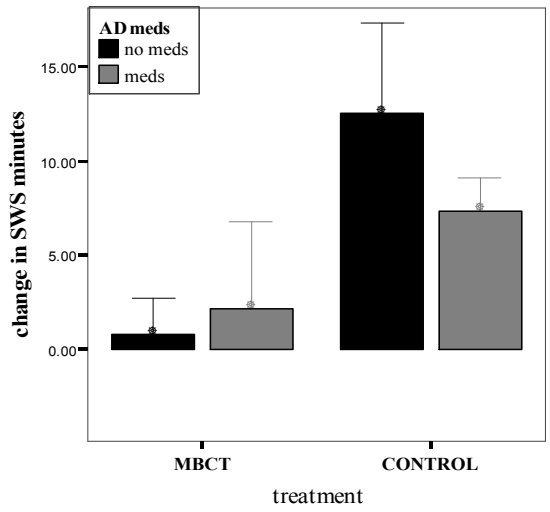

AD meds
no meds
meds
15.00
10.00
5.00
0.00
change in SWS minutes
MBCT
CONTROL
treatment

Figure 4

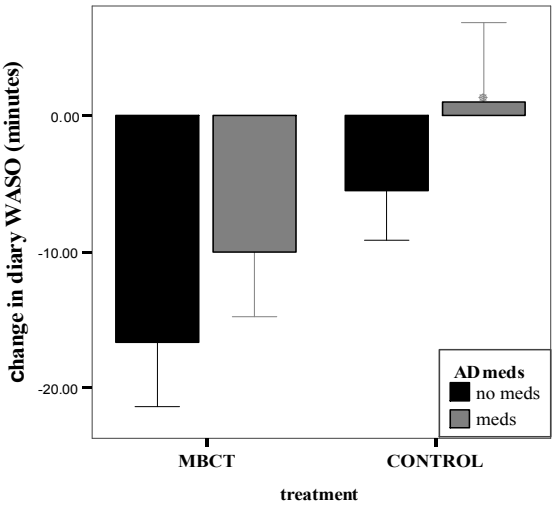

change in diary WASO (minutes)
0.00
-10.00
-20.00
AD meds
no meds
meds
MBCT
CONTROL
treatment

Figure 5

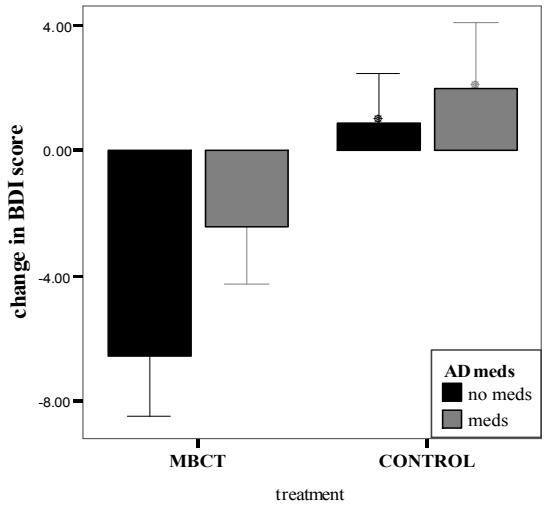
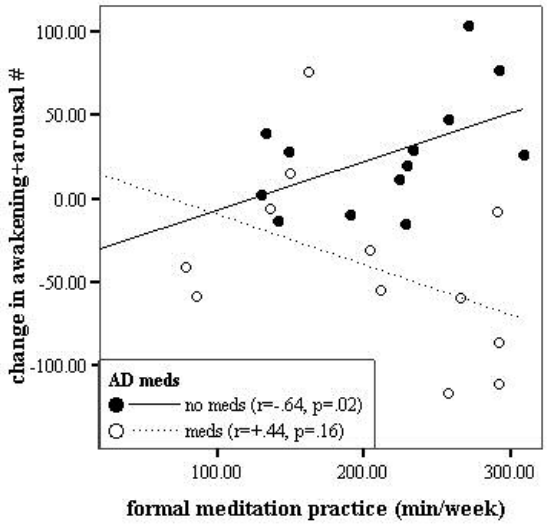

4.00
0.00
-4.00
-8.00
change in BDI score
AD meds
no meds
meds
MBCT
CONTROL
treatment

Figure 6


100.00
50.00
0.00
-50.00
-100.00
change in awakening+arousal #
AD meds
no meds (r=-.64, p=.02)
meds (r=+.44, p=.16)
100.00
200.00
300.00
formal meditation practice (min/week)