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Mindfulness Meditation, Aging, and Cognitive Function

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A Systems Approach to Stress and Resilience in Humans: Mindfulness

Meditation, Aging, and Cognitive Function

by

Barry S. Oken

A dissertation submitted in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy
in
Systems Science

Dissertation Committee:
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Portland State University
2016

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Abstract

Psychological stress is common and contributes to many physical and mental health problems. Its effects are mediated by a complex neurobiological system centering in the brain with effectors including autonomic nervous system, hypothalamic-pituitary-adrenal axis, inflammatory system, and gene expression. A stressor pushes the human physiological system away from its baseline state towards a lower utility state. The physiological system may return towards the original state but may be shifted to a lower utility state. While some physiological changes induced by stressors may benefit health, chronic stressors usually have negative effects on health. In contrast to this stressor effect is the system's resilience which influences its ability to return to the high utility attractor basin following a perturbation by increasing the likelihood and/or speed of returning to the baseline state following a stressor.

Age-related cognitive decline is a major public health issue with few preventative options. Stress contributes to this cognitive decline, and mindfulness meditation (MM) is a behavioral intervention that reduces stress and stress reactivity in many health conditions. A randomized clinical trial was performed to determine if MM in older adults would improve measures of cognitive function, as well as psychology and physiology, and to determine what factors might predict who would improve. 134 at least mildly stressed 50-85 year olds were randomized to a MM intervention or a wait-list control. Outcome measures included a broad cognitive function battery with emphasis on attention and

executive function, self-rated psychological measures of affect and stress, and physiological measures of stress. Self-rated measures related to negative affect and stress were all significantly improved as a result of the MM intervention compared to wait-list control. There were no changes in cognition, salivary cortisol, and heart rate variability. Potential explanations for the discrepancy between the beneficial mental health outcomes and lack of impact on cognitive and physiological outcomes are discussed.

To determine which factors predict MM responsiveness, a responder was defined by determining if there was a minimum clinically important improvement in mental health. Predictors included demographic information and selected self-rated baseline measures related to stress and affect. Classification was performed using decision tree analysis. There were 61 responders and 60 non-responders. Univariate statistical analysis of the baseline measures demonstrated significant differences between the responder and non-responders in several self-rated mental health measures. However, decision tree was unable to achieve a reliable classification rate better than 65%.

A number of future research directions were suggested by this study ,including to optimize the MM intervention itself, to better select participants who would benefit from MM, and to improve the outcome measures perhaps by focusing on decreased reactivity to stressful events. Finally, a less well-defined but always present future research direction is the development of better models

and better quantitative analysis approaches to the multivariate but dynamically limited human empirical data that can be practically collected.

Dedication

To my wife, Melanie, who is my strongest supporter, worst critic and helps ensure my language and communication skills are acceptable, and to my children Kiva, Adam, and Corey whose impressive amount of learning over their last ten years provided incentive to me to increase my learning as well.

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The next generation of researchers including those I mentor who will helpfully be able to use some of this knowledge to pursue their projects.

Friends and colleagues who were supportive even if occasionally wondering why I was pursuing this PhD. To the modern statistician who offered me the critical advice that the information I asked about is on the web and I should simply search for it.

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Chapter 1.

Introduction

The motivation for this research is to be able to better evaluate the effect of a stress-reducing therapy, mindfulness meditation (MM), in a group of older adults. The relationship between age-related cognitive changes and stress, and the remediation of those cognitive changes with a stress-reducing intervention, MM, is the focus of the research analyses of this dissertation. Chapter 1 provides a focused background for the research and some details about the data that will be analyzed in chapters 3 and 4. Chapter 2 consists of a more complete review and synthesis of the literature concerning a systems approach to stress and resilience in humans based on a just-published paper by the candidate. Chapters 3 and 4 are papers that utilize specific analytic techniques to analyze data that were obtained over the last 5 years as outlined in chapter 1. Chapter 5 is a synthesis and discussion chapter. Some text in the introduction/background and methods sections in Chapters 3 and 4 are repetitions but are important to ensure the chapters can stand-alone for journal publication.

Age-related cognitive decline is prevalent with significant cost to society and very limited preventions. The prevalence of cognitive decline associated with functional impairment, dementia, is about 14% of Americans over 71 years old.[1] The cost to the US is around \$200 billion.[2] Cognitive impairment without dementia in those over 71 is even more prevalent, about 22%.[3] Despite the personal and societal cost and known epidemiological risk factors such as

hypertension or low education, there are no evidence-based recommendations for prevention of age-related cognitive decline.[4] There is an urgent need to develop prevention strategies extending beyond pharmacological and dietary supplement approaches. Mildly improving cognition and delaying the onset of dementia by 6 months with a widely available behavioral intervention would decrease the number of dementia cases by over 100,000 over a 10-year period.[5]

Older adults are more likely to develop cognitive symptoms from medical conditions. In addition to slowly progressive cognitive decline, older adults are much more likely to develop significant but transient cognitive impairments even to the point of delirium. Overall brain function weakening could be caused by depression, nutritional defects, oral or anesthetic medications with central nervous system effects, or simple hospitalization.[6-8] This highlights that older adults are more susceptible than younger adults to any process that negatively affects brain function. Developing strategies to decrease the negative impact of depression and stress contributing to age-related cognitive decline is the rationale for this research.

Psychological stress is very common and contributes to health problems. 25% of surveyed American adults reported high stress and 50% reported a major stressful event over the past year according to a 2014 survey.[9] While health

problems contributed to stress, mundane daily activities also contributed. The top three were juggling family schedules, hearing about what the government or politicians are doing, and reading or listening to the news. Stress is caused by any event with **N**ovelty, **U**nexpectedness, **T**hreat to ego, or **S**ense of not being in control (NUTS).[10] Stress directly costs society through decreased work productivity and increased sick days. Chronic psychological stress also affects the underlying pathophysiology or stress-related symptoms contributing to a broad range of diseases such as cardiovascular health,[11-14] neurologic and psychiatric diseases such as epilepsy,[15] Parkinson's disease,[16-18] multiple sclerosis,[19, 20] eating disorders, and addictions.[21] Stress may also worsen behavioral symptoms such as anger and thus, may symptomatically worsen disorders such as traumatic brain injury, Post-Traumatic Stress Disorder (PTSD) and dementia. Therefore, evidence-based approaches that reduce psychological stress will improve population health.

Psychological stress and reactivity to stress contributes to age-related cognitive decline. Not only does psychological health affect general health, it also affects brain health specifically. Chronic psychological stress contributes to cognitive decline, hippocampal injury, and neurodegenerative diseases either directly or through stress mediators.[14, 22-27]. The negative effect of psychological stress on cognitive function may be greater with aging [28-31]. Higher reactivity to negative events produces physiological changes.[32] In fact,

negative reactions to events are more predictive of emotional well-being than the event itself.[33] Neuroticism, i.e., elevated stress reactivity associated with negative emotions, has genetic, neurobiological, and environmental contributions.[30, 34, 35] High neuroticism contributes to many health disorders[36] and is linked to increased age-related cognitive change and clinical Alzheimer disease (AD) in longitudinal studies (although the neuropathology of this cognitive change or clinical dementia syndrome is not related to amyloid deposition).[37-39] The cognitive deficits related to proneness to distress are not specific and most consistently include frontal-executive function and perceptual speed,[37, 39] similar to cognitive changes associated with affective disorders such as PTSD and depression.[40, 41] Neuroticism with its negative effects on cognition is a modifiable risk factor[42] with a potentially large impact on population health.[43]

Resilience to stress can be protective and can be learned. While high reactivity to stress can be detrimental to one's health, resilience to stressors can be protective. Resilience is the ability an individual's physiology and psychology to avoid a diseased/disordered state and/or to return to a baseline state more quickly following a stressor. *Resilience* has been used quantitatively in systems science for decades.[44] However, the adaptive neuroplastic responses underlying human resilience are just beginning to be understood from the neurobiology perspective.[45] Depression and stress produce increases in

amygdala reactivity and size and decreases in hippocampal and frontal cortex size; resilience to stress might be a marker for neuroplasticity associated with interventions such as meditation training.[41, 46] Individuals respond differently to similar negative stressors. Resilience to psychological stress is associated with no prior history of depression, male gender, lower neuroticism, and high self-esteem and results in decreased incidence of significant psychopathology, such as PTSD or major depression, when exposed to a stressor.[47-50] Similar protective characteristics such as self-efficacy, personal mastery, and coping, are associated with resilience to the stress of dementia caregiving.[51]

Aspects of resilience are also important for minimizing cognitive decline but this has been underexplored from both the intervention and neurobiology perspective. Applying the definition of resilience to AD, we could call the brain insult or stressor AD pathology and the disordered state, dementia. Thus, resilience to AD pathology can be demonstrated by similar amounts of AD pathology producing variable cognitive decline. Characteristics of resilience to the AD pathology could include cognitive reserve,[52] larger brain or hippocampal size,[53] compensatory ability while performing cognitive tasks,[54] lesser amounts of co-existing white matter pathology associated with cerebrovascular pathology,[55, 56] or preservation of neuron numbers, synaptic markers and axonal geometry.[57] Any intervention that could improve resilience to stress may favorably influence cognitive decline. While psychophysiological resilience to laboratory stressors has been widely used, e.g.,[58, 59] the

experimental reactivity to stressors has not been as widely evaluated using fMRI.[60-64]

Low doses of a stressor may improve the resilience of the physiological system[65, 66] Exposure to low doses of stressors reduces stress reactivity, whether the stressor is exercise[67] or caloric restriction.[68] Psychophysiological and cortisol responses to stress have been altered by cognitive behavioral therapy[69] and stress management programs.[70] Decreased prefrontal control of emotional reactivity is present in depression and can be altered by cognitive behavioral therapy[40] and meditation (see below).

Mindfulness Meditation (MM) interventions may support cognitive function in older adults and reduce reactivity to stress and increase resilience. A behavioral intervention such as meditation that could reduce reactivity to stress and increase resilience in older adults may improve cognitive decline and thus reduce overall health costs and burden in the US. Mind-body medicine, such as meditation and yoga, is the most commonly used type of complementary and alternative medicine treatment[71] and it attempts to modify individuals' stress responses.[72, 73] A recent NIH survey shows that more than 20 million U.S. adults practice meditation for health. While meditation practices have different areas of emphasis,[74] MM shows promise in many health conditions. MM is popular and teaches skills applicable to everyday life situations.[74] A key facet of MM is attending to the present moment in a non-judgmental way. MM

intervention has already been formally studied and applied in a variety of clinical conditions including PTSD, depression, pain, and stress.[75-85]

Meditation decreases negative affect and increases positive affect and resilience. MM is an acceptable and evidence-based treatment for stress and depression.[86, 87] Mindfulness has several components.[88, 89] The non-judgmental component or not reacting overly emotionally to external or internal events is an important aspect of MM training and is directly related to negative affect. We have found this non-judgmental component to differ in those with chronic stress, i.e., veterans with compared to veterans without PTSD,[90] and older adults who are dementia caregivers compared to age-matched non-caregivers.[30] Positive affect, which is not simply the opposite of negative affect, may be also improved by meditation.[46, 91, 92] Meditation also decreases reactivity to computer game stressors,[93] Trier Social Stress Test,[94, 95] and a film stressor[96] in younger adults.

Meditation is associated with improved cognitive function. Most cognitive and neuroimaging meditation studies have been uncontrolled or cross-sectional (comparing experienced to beginner meditators or non-meditators).[97] The cognitive outcome studies with younger adults and RCTs are limited.[98-105] Regardless, attention and executive function improvement has been suggested. A recent systematic review of meditation effects on age-related cognitive decline

in older adults[106] found only 6 studies including an earlier study of the candidate's, a dementia caregiver study.[107] The improvements on clinical neuropsychological tests observed in these studies were usually in the frontal-executive function domain, such as the Stroop task where participants report the color in which a color-word is written and not simply read the color-word ("blue" written in red ink should be reported as "red" and not "blue") [108] and Trails where participants alternate connecting by pencil sequential letters and numbers but alternating them (A – 1 – B – 2 – C – 3 ...). Meditation likely produces its cognitive benefits through two mechanisms: 1) improving cognition by decreasing levels of stress and/or stress reactivity or 2) improving attention through attention training. (These two mechanisms are not mutually exclusive.) While meditation holds promise for improving cognitive function more research is needed. We will focus on meditation reducing stress and improving resilience for improving cognition in older adults.

Meditation has produced changes in neuroimaging: structural and functional MRI in younger adults. As noted above with cognitive function, most meditation structural neuroimaging research consists of cross-sectional or uncontrolled pre- and post-meditation training comparisons.[109] As with structural imaging, few RCTs evaluate physiological changes of meditation using either EEG, event-related potentials or fMRI.[110-112]

Who benefits from meditation? Despite reported improvements following meditation interventions, there has been little research into who benefits from meditation. Given the complexity of the stress system including its interaction with much of human physiology, it would be helpful to know what factors might predict clinically significant improvements from meditation since it is likely that some people benefit significantly while others may not benefit at all. At least some measures of affect impact on response to meditation treatment. People with panic disorder receiving mindfulness-based cognitive therapy demonstrated greater improvements in their panic disorder symptoms if they were less depressed at baseline based on Hamilton Depression Rating Scale. [113] Since regression to the mean is one confound when determining responsiveness to treatment, in part explaining some reported placebo effects [114], the fact that the less depressed people responding more suggests an alternative explanation.

Summary of background and rationale for research. There is evidence that excessive stress causes cognitive and brain changes and that meditation practice can reduce levels of stress. There is less evidence that meditation reduces physiological stress reactivity and very limited evidence that meditation may improve cognitive function in older adults. It is not known whether the cognitive function of older adults can be improved with meditation and this is of very high significance, even if the improvement is only moderate. It is also not known how reactivity to stress contributes to cognitive change. Understanding

how stress contributes to cognitive change and how decreased stress might improve cognition would be of high significance to guide strategies that maximize cognitive health in aging. From a Systems Science perspective, there are many interacting variables measured over time with unclear relationships. It is important to utilize analysis methodologies that can capture as much of the dynamic aspects of the data as possible.

Data collection for this dissertation was done under the direction of the candidate while he was enrolled in the Portland State University Systems Science PhD program. Two research assistants working directly under the candidate's supervision collected the data and another research assistant provided the MM training intervention. There was no external funding for this particular research project although the candidate's NIH K24 award for career development provided some salary support for the candidate and 50% salary support for a single research assistant.

METHODOLOGY

Participants consisted of generally healthy adults 50-75 years of age who reported at least mild stress. Further inclusion and exclusion criteria as well as recruitment information are provided in chapter 3.

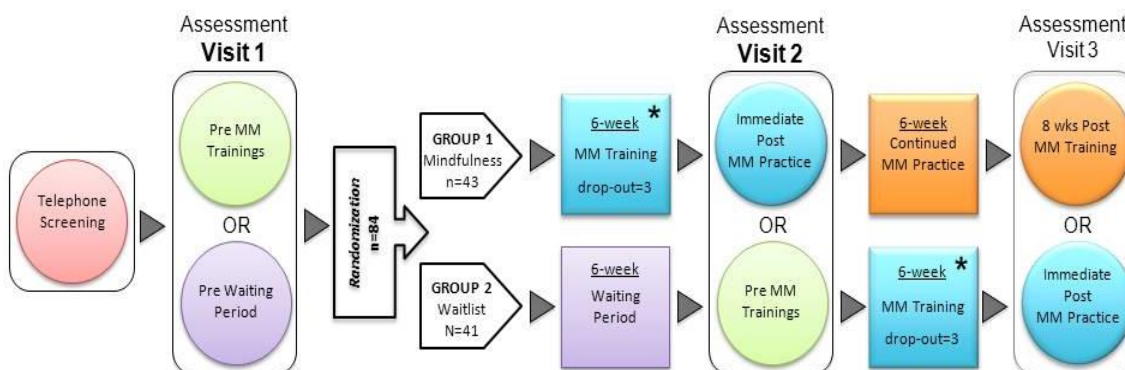


Figure 1.1. Schematic of participant visits and study flow

There were three testing visits (Figure 1.1), each 2 months apart, and participants received a 6-week mindfulness meditation (MM) intervention either between Visits 1 and 2 or between Visits 2 and 3. Participants who received the intervention directly after Visit 1 were encouraged to continue meditating between Visits 2 and 3, and participants who received the intervention post-Visit 2 served as a wait-list control. The outcome measures include: 1) self-rated measures of stress and affect; 2) measures of cognitive function, and; 3) physiological markers of stress. Further information regarding the rationale and the specific measures are provided in chapters 3 and 4. Several self-rated stress/affect measures and a single cognitive function measure were obtained at each visit using ecological momentary assessment (EMA) that made assessments using a smartphone at four time points over a 24-hour period excluding sleep times at the time of each visit while the participants were in their usual environment.

Intervention

The MM intervention was administered in six, one-on-one sessions occurring weekly either between visit 1 and visit 2, or between visit 2 and visit 3 (wait-list control). The intervention also involved recommended daily home-practice. An unblinded RA delivered the training sessions but the assessments were performed by blinded RAs. Having only a wait-list control implies that some benefit of the MM compared to wait-list may be related to placebo effects [115] but this study was done with limited funding. Below is a brief description of the MM intervention and wait-list control condition. Participants who were randomized to the wait-list arm between visit 1 and visit 2 received the MM intervention after the wait-list period (between visit 2 and visit 3). Adherence for the MM intervention was assessed using a study iPod.[116]. All participants met weekly with the unblinded RA during the active 2-month intervention block and at the halfway point in the other 2-month block to help minimize drop-outs.

Assessments (Table 1.1)

Outcome assessments were done at each visit. More details are given in Chapter 3.

Table 1.1. Assessments at the three visits

Assessments	Visit 1	Visit 2	Visit 3
	(baseline)	(2	(4
		months)	months)

Cognitive assessments	X	X	X
Other physiological measures (EEG, ECG, bp, respiration rate, cortisol)	X	X	X
Questionnaires: e.g., stress, neuroticism, mood, fatigue, mindfulness, & resilience	X	X	X
Smartphone ecological momentary assessment	X	X	X
Adherence (paper log and study iPod)		X	X
Expectancy/Credibility	X		

Cognitive Assessments were based on prior studies and focused on frontal/executive function but also included episodic memory, working memory, and reaction time. At all visits, participants were assessed with self-rated measures that might interact with or mediate the MM intervention effect, including stress, neuroticism, mood, fatigue, self-efficacy, sleep quality, mindfulness, resilience. Physiological assessments include EEG, heart rate and heart rate variability, and salivary cortisol. Expectancy and Credibility assessments were performed to determine if expectancy impacted any improvements observed from the MM intervention.

The next chapter expands on this Introduction to focus on the human stress system trying to integrate knowledge of the physiology of the stress system with knowledge from systems science.

Chapter 2

A systems approach to stress, stressors and resilience in humans

Published in Behavioural Brain Research 2015, 282:144-154, authors B.S. Oken, I. Chamine, and W. Wakeland

Abstract:

The paper focuses on the biology of stress and resilience and their biomarkers in humans from the system science perspective. A stressor pushes the physiological system away from its baseline state towards a lower utility state. The physiological system may return towards the original state in one attractor basin but may be shifted to a state in another, lower utility attractor basin. While some physiological changes induced by stressors may benefit health, there is often a chronic wear and tear cost due to implementing changes to enable the return of the system to its baseline state and maintain itself in the high utility baseline attractor basin following repeated perturbations. This cost, also called *allostatic load*, is the utility reduction associated with both a change in state and with alterations in the attractor basin that affect system responses following future perturbations. This added cost can increase the time course of the return to baseline or the likelihood of moving into a different attractor basin following a perturbation. Opposite to this is the system's resilience which influences its ability to return to the high utility attractor basin following a perturbation by increasing the likelihood and/or speed of returning to the baseline state following a stressor. This review paper is a qualitative systematic review; it covers areas most

relevant for moving the stress and resilience field forward from a more quantitative and neuroscientific perspective.

Keywords: psychological stress, systems science, allostatic load, resilience

Abbreviations

ACTH: adrenocorticotrophic hormone

ANS: autonomic nervous system

DHEA: dehydroepiandrosterone

DHEAS: dehydroepiandrosterone sulfate

EEG: electroencephalogram

fMRI: functional **magnetic resonance imaging**

HgbA1c: glycosylated hemoglobin A1c

HPA axis: hypothalamo-pituitary-adrenal axis

HRV: heart rate variability

PET: positron emission tomography

PTSD: post-traumatic stress disorder

SSRI: selective serotonin reuptake inhibitor

1. Introduction

Psychological stress is common in our society. A recent survey indicated that 25% of Americans reported high stress and 50% identified a major stressful event during the previous year [9]. Chronic psychological stress increases risk of health problems and contributes to cardiovascular problems [11, 117], neurologic and psychiatric diseases such as epilepsy [118], Parkinson's disease [17], multiple sclerosis [19], eating disorders, addictions [21], post-traumatic stress disorder (PTSD), and sleep difficulties. Therefore, it is important to develop evidence-based methods that minimize stress impact. A fuller understanding of stress physiology and psychology can be achieved by approaching this topic from different angles. This work offers a review of stress physiology and psychology from a systems science perspective.

Systems science is a methodology used to understand complex systems from organizational, structural, and dynamic perspectives.[119] From a systems science viewpoint, stress often corresponds to a state away from optimal in a dynamical system where the optimal location represents a high utility attractor. An attractor basin in a dynamical system corresponds to the conceptual space of locations in which the system resides over time. The state of stress results from a perturbation arising from the internal or external environment (stressor). This stressor could result in the system returning to the baseline optimal attractor or moving into a lower utility attractor basin. The attractor basin is the region of space that shares the same attractor and the whole space may have multiple

attractors (Figure 2.1).

The attractor in the human system is not a fixed point attractor given the multidimensional nature and, almost inherent, within-subject temporal variability of the physiological measures of state. The noise present in the measurement of the many variables constituting the human system implies the observed human system is stochastic; thus, the attractors are very difficult to describe. In addition, given the varying time frames over which the components of the human physiological system change, the terms *state* and *variable* describing more immediate changes and the terms *trait* or *parameter* describing longer time frame changes represent an artificial separation of the various physiological measures that have different units and widely distributed half-lives. Whatever the attractor, even if the system returns to the baseline high utility attractor, there is often some underlying cost. This cost to the system is a change in the underlying physiology that may: 1) decrease the rate of return to the high utility attractor or 2) decrease the likelihood of returning to the optimal attractor following a future stressor perturbation because the size of the attractor basin is smaller or the attractor has moved closer to a boundary with a non-optimal attractor basin. The movement of the dynamical system into a different attractor basin could also be due to a single severe stressor potentially via a dynamical system catastrophe, for example, development of PTSD following a single event (Figure 2.2).

Besides negative effects, the stressor can also induce beneficial changes leaving the system more resilient to future perturbations, i.e., cause the opposite of 1) and 2) above. The term *resilience* includes several conceptual aspects.

Resilience refers to how effectively and quickly the system returns to baseline.[44] This includes whether the human dynamical system avoids moving to a lower utility disease state following a stressor.[45] A related term is *stability* which refers to how well the system can maintain its current high utility condition without being pushed away.

Although a stressor may cause a short-term decrease in some measure of utility, sometimes it results in longer-term utility increase. In the case of humans, this is related to learning as discussed below. The human dynamical system may experience some low-stress environmental perturbation that results in a relatively immediate gain in reward or utility, e.g., obtaining food when hungry or some longer-term gain in utility, e.g., the brain acquiring a better understanding of the environment. There is an apparent inverted u-shaped effect of stress on longer-term utility, such that occasional small amounts of stress may improve both short- and long-term utility but experiencing no stress or large amounts of stress may have negative long-term effects on the organism. Though the term “human” will be used, most of this discussion applies to other animals and to systems in

general.

2. The human physiologic system: brain structure and network (Figure 2.3)

A human is a dynamical system composed of subsystems that help maximize utility of the organism. Utility may be defined: 1) from a purely biological perspective such as immediate reproductive success or obtaining food, or 2) from a more complex, perhaps hedonic or longer-term perspective such as longer-term reproductive success, obtaining more resources, gaining group support or enjoying an amusement park ride. Longer-term utility could extend beyond the lifespan, e.g., survival of the related social unit or the entire species (see section 9 for more information about utility). The organism is maintained by many critical systems and subsystems, such as cardiovascular and renal, but this paper focuses on the brain dynamical system and its communication links with the body via autonomic nervous system (ANS), hypothalamo-pituitary-adrenal (HPA) axis and neuroimmune system. The limbic system is involved in psychological aspects of stress, including neocortex activation by emotional states and memories of events associated with emotional valences. Older and more caudal brain parts including the brainstem and spinal cord are generally not critical for the following discussion with some exceptions including ANS components. The sympathetic portion of the ANS involving central catecholaminergic systems is particularly important for communicating the brain

perception of stress to the whole body by causing changes such as increased blood pressure and heart rate. The hypothalamus is an important communication link secreting neurohormones, e.g., adrenocorticotrophic hormone (ACTH). Given this background, the most commonly discussed physiologic responses to a stressor involve the HPA axis, the locus coeruleus-norepinephrine-sympathetic nervous system pathway, the parasympathetic system, the immune system, and gene expression and alterations including epigenetic changes.

The two-way communication between the major effector systems (ANS, HPA, and immune) and the brain exist in part to ensure the stress-related systems provide feedback for learning and help avoid over-reactivity. The communication system between the immune system and the brain constitutes an entire field itself, psychoneuroimmunology.[120] The immune system - brain communication is significantly mediated by cytokines. All these two-way communication systems directly impact the brain via its receptors for norepinephrine, ACTH, cortisol, and cytokines, with prefrontal cortex, hippocampus, and amygdala being most prominent.[121] Feedback is often inhibitory and is not perfect. Occasional errors in this two-way communication system may arise. For example, a major increase in heart rate in an exercising older adult with atherosclerosis might be accompanied by an attempt to decrease the heart rate, but this decrease may be insufficient to prevent a myocardial infarction and even a sudden death.[122] Additionally, the awareness of stress may itself be a stressor; however, this type

of stress is distinct from experiencing external environmental stressors. Stress awareness may be commonly related to the “recall” or association of particular environmental inputs with prior stress.

3. Stressor

A stressor is an environmental event that significantly perturbs the entire human dynamical system away from the optimal attractor resulting in a state of lower utility. The stressor may move the physiological system to a different attractor basin, move the system state closer to the edge between its current attractor basin and another attractor basin of the physiological system (“precariousness”), or slow the rate at which the system returns to the optimal attractor. The movement of the system is not dependent solely on objective measures of the stressor but also on the individuals’ traits of distress proneness and their perceptions of the stressor. If the perturbation is perceived to impact an organism negatively or associated with obvious threats (hunger/visualization of aggressor), there is an immediate effect to reduce the likelihood of a negative stressor impact. For example, seeing a bear with her cub while hiking will generate physiological changes important for action (elevated heart rate and blood pressure) and increased attention to environmental stimuli, thus improving encoding of the situation for future recollection. These perturbations increase likelihood of survival over the short-term but if maintained long-term may have deleterious effects. For example, a transient increase in blood pressure is

tolerable and may be helpful, but a chronic increase in blood pressure is not high utility. Stress doses that are not high enough to cause significant health problems such as disease or death from a state change may produce higher average utility within the basin by altering the shape of the basin or by moving to a different, higher utility basin. In an athletics example, both short-term stress at an Olympic competition and longer-term stress from high effort athletic activity over a training period may improve athletic performance. However, excessive or repeated perturbations may have a cost to the underlying system that outweighs the benefit.

Stressors may include external environment perturbations such as extreme heat or icy roads while driving. Stressors may also include internal environment perturbations such as infections or elevated glucose. Stressors may be predominantly psychological and mediated by brain perception and future expectancy. Stressors are not necessarily physical changes in the environment but may involve loss of a significant relationship, financial stress, negative neighborhood characteristics, or social threats including discrimination [123-126].

For most of this discussion, the stressor referring to perturbations under tight physiological control will be omitted. Information signals from these perturbations such as alterations in serum sodium do not need to reach the brain level to be

regulated. *Homeostasis* refers to the dynamic control of these state variables maintained within a narrow window for humans to successfully function. The dynamical system representing the whole person is regularly exposed to more heterogeneous stressors than serum sodium changes, including potential stressors that are anticipated. *Allostasis* has been used to describe “actively maintaining homeostasis” [27], but the practicality of this distinction from *homeostasis* is uncertain [127].

Some stressors represent state perturbations to which the person may respond without any obvious long-term negative ramifications. Some stressors, in part related to their chronicity, may have negative long-term ramifications. The perturbation may induce changes in several systems. For example, as time passes from the previous meal, a human’s stomach is growling and blood sugar is getting lower; the brain senses hunger and mobilizes to address the perturbation stressor. Part of the response to a stressor will be mediated directly by the internal environment without requiring any mediation by the brain, e.g., hunger causing the release of hormones to break down glycogen. Part of the response is directly mediated by the brain responsible for planning how to interact with the external environment, e.g., walking into the kitchen to get food. The perturbation may induce changes in physiological parameters, e.g., DNA transcription or epigenetic modifications to alter neurotransmitter receptor sensitivity. Responding to these stress perturbations may induce some cost to

the system. This cost may involve the movement of the system into another basin of attraction or an increase in the probability that the system will move into another basin following future perturbations.

Though the stressor has some objective qualities, it can be difficult to quantify because physiological stress effects are highly dependent on the subjective perception. Quantifying an individual's stressors has been attempted [128]. Some examples of stressors include events that have novelty, unpredictability, (any information-rich input beyond the brain processing ability), threat to one's ego, or sense of loss of control (NUTS) [129]. Short-term laboratory experimental stressors are related to these NUTS concepts including the Trier Social Stress Test, [130], the Montreal Imaging Stress Task [131], titrated Stroop color-word interference task [132], physical (e.g., putting a hand in ice water) [133], or perceptual stressors (e.g., the disturbing pictures of the International Affective Picture Scale [134]). Stress responses can also be conditioned [135] allowing for comparison between humans and other animals. It is more challenging to study long-term stressors experimentally but occasional misfortunes such as wars and other disasters have generated informative epidemiological data, e.g., the World Trade Center disaster. Stressors may involve awareness of a stressor, even if it is erroneous, e.g., misperception of an environmental change. Relevant examples include erroneous stress associations with ordinary loud sounds that have developed from explosion-related PTSD or a pheochromocytoma producing

a surge of catecholamines perceived as a stress state because of diaphoresis and a fast heart rate.

In general, frequent perturbations into a stressed state away from the high utility attractor have a cost to the system. The cost of going to the refrigerator when feeling hungry is low. However, a related perturbation, the blood sugar increase and the need to secrete insulin due to overeating high-sugar items may eventually cause long-term negative effects. If repeated enough, it may diminish the human's ability to stay in a positive functional attractor, and the lack of responsiveness to insulin at the cellular level (i.e., insulin resistance) may cause adult type 2 diabetes. This common stress-related change has resulted in a common diabetes measure, glycosylated hemoglobin HgbA1c, frequently used as a chronic stress biomarker. In humans, *allostatic load* is the cost to the system due to repeatedly returning to baseline, i.e., the costs of executing the physiological changes and the potential costs of making the changes in architecture of the basins of attraction (their size, depth, etc.) following a stressor as well as the eventual impacts of the architecture change. *Allostasis* has been used to describe the dynamical control over these variable perturbations for maintaining a functional state. Though there is some controversy over whether allostasis is truly different from homeostasis [127], the term *allostatic load* has been used as a conceptual measure of the physiological cost due to chronic

stressors [136] and will be used in this paper. Attempts to define a metric of allostatic load for experimental use are discussed below.

4. Measurement of stress

The term stress describes a state of physiologic and behavioral responses to a stressor with the brain being the critical interpreter of what is stressful. Though inconsistently used, the stressed state in humans for the purposes of this discussion is linked to dynamical physiological change. The stressed state also involves the conscious and unconscious stressor interpretation by the brain including the conscious perception of the stressors and the perception of the physiologic response generated by the stressor [137-139]. Stressors result in changes in state variables and parameters and have been measured using various biomarkers.

There are many objective ways to measure human stress responses other than commonly used self-rated scales. As previously noted, physiologic responses to stress include activation of the HPA axis, activation of the locus coeruleus-norepinephrine-sympathetic nervous system pathway, the parasympathetic system, immune system, and genes [137, 139-143]. Importantly, the timing of these changes is variable. When measured as state variables, they may or may not shed light on the dynamical nature of the physiologic system, resilience, or

allostatic load. Dynamical aspects of stress and resilience may be estimated with repeated measurements over longer periods during daily routines or following a known experimental stressor.

4.1. Peripheral biomarkers

Each biological assessment has a sampling time window. For example, a peripheral blood draw to assess cortisol reflects cumulative changes over minutes, cortisol overnight urine collection measure reflects cumulative changes over hours, and a hair sample may reflect cumulative changes over months.

HPA axis activity biomarkers include glucocorticoids: free cortisol (or corticosterone in experimental animals), ACTH, and corticotropin releasing hormone [144, 145]. In addition to acute stressor-induced changes in these biomarkers, there are alterations in diurnal fluctuations with chronic stress, e.g., in cortisol awakening response [85, 146]. Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) act to counter-regulate cortisol [147]. DHEA is used as a stress marker by itself [148] or as a ratio to cortisol and has been affected by depression [149]. Mineralocorticoids may also be stress biomarkers [150].

Several autonomic activity measures are associated with acute or chronic stress

including blood pressure, electrodermal response, skin temperature, respiratory rate, heart rate and heart rate variability (HRV) [151]. A variety of HRV measures in the time and frequency domains have been evaluated [152, 153]. While HRV may look at dynamical changes over long periods, e.g., 24 hours or more, longer-term HRV requires more sophisticated data processing to correct for exercise and unrelated to stress activities modifying the heart rate.

Many measures correlated with stress have been treated as relatively static measures. There are alterations in immunologic function including cytokines; gene and epigenetic modifications involving telomere changes; and metabolic activity fluctuations resulting in generation of reactive oxygen and nitrogen species damaging to cellular structures [137, 141, 143, 154-156].

There are other biomarkers not directly related to the currently discussed physiological stress pathways. To assess stress responses researchers have used measures of muscle activity e.g., using electromyographic activity for biofeedback in treatment of muscle contraction and other types of headaches. Biofeedback has been used on many physiological measures with only few (peripheral temperature and electrodermal activity) being closely related to ANS activation [157]. Additionally, as many have casually observed, stress alters voice characteristics [158] and posture in a chair [159]. Other biomarkers are

listed below under allostatic load.

4.2. Brain changes

4.2.1. Cognition

Cognitive function including memory is significantly altered by stress in humans and non-human animals [117, 160, 161]. Cognitive decline associated with stress (and the closely related construct depression) may affect speed, attention, and executive function [117, 162]. Prefrontal cortical dysfunction is particularly impacted by stress [163]. This pathological relationship becomes more evident with age [28], and highly stressed elders such as dementia caregivers may be particularly at risk [155].

4.2.2. Structural brain changes

Stress-related states such as PTSD and fear conditioning are linked to decreased hippocampal size, decline in prefrontal cortex, increased size of portions of the amygdala, and decreased inhibition of the amygdala and related brain regions by the frontal lobes [161, 163-165]. The brain changes are at least partially mediated by cortisol with increased cortisol related to smaller hippocampi [166]. The time course of structural change is much longer than the half-life of cortisol; cortisol elevation needs to be sustained to cause longer-

lasting brain changes. Smaller hippocampi are common among people with PTSD or trauma exposure [167, 168] and they also are linked to increased risk for PTSD development [169] so the causative relationship is uncertain. Further, PTSD sufferers are at higher risk of dementia [170] and those with smaller hippocampi have increased the risk of dementia [171]. Therefore, defining the causative aspects of these relationships is critical and can affect other important health concerns. From the perspective of beneficial effects, research shows increased hippocampal volume and improved verbal declarative memory in PTSD patients after using a selective serotonin reuptake inhibitor (SSRI) antidepressant for 9-12 months [172]. This is likely related to SSRI-related neurogenesis increase [173].

4.2.3. Physiological brain changes: *EEG, event-related potential, fMRI*

EEG stress-related changes, particularly frontal asymmetries [174, 175], and alterations in event-related potentials [176] have been noted, but these changes have not been consistent, in part due to lack of distinction between state and trait markers and limitations in signal processing [177]. Chronic psychological stress impairs sleep and the resultant sleep deprivation may impact EEG. PET and fMRI detect brain activation changes due to experimental stressors [63, 178, 179].

4.2.4. Genetic changes in brain

There are different functional gene classes that underlie the diverse effects of glucocorticoids on brain function, e.g., energy metabolism, signal transduction, neuronal structure, and neurotransmitter catabolism [140]. Stress effects on telomeres have been mentioned but assessments of human telomeres are generally performed on peripheral blood limiting their direct brain association.

4.3. Allostatic load

The underlying biological definition of allostatic load is very broad since the physiological system represents a highly multidimensional state space with many parameters. Potential examples of underlying load include the cost of gene transcription, metabolic activity, and alteration in cell receptor sensitivity.

Frequent DNA processing may produce changes in telomere length.

Allostatic load was originally developed as a composite marker of chronic stress-related disequilibrium generated from a number of physiological measures. The originally described allostatic load score was a composite of 10 measures (systolic and diastolic blood pressure; waist-hip ratio; ratio of total cholesterol to high density lipoproteins; high density lipoprotein cholesterol; glycosylated hemoglobin; overnight 12-hour urinary cortisol, epinephrine and norepinephrine;

and DHEA-S [180]. The score obtained by summing the ten measures (0 if normal, 1 if 75th percentile or worse) was associated with mortality. Related composite allostatic load measures have been correlated to childhood poverty [181] and measures of work exhaustion [182]. The latter study added several measures (tissue necrosis factor-alpha, C-reactive protein, fibrinogen, and D-dimer) and other measures have also been added, e.g., pro-coagulant activity. Despite the widespread interest in allostatic load, the optimum measure has not been defined; the measures currently used are based on non-experimental approaches (e.g., simple availability and a priori rationales). As a result there is much variety in the definition of a composite measure [183], but there needs to be improvement in its definition to advance the field of biomarkers for chronic psychological stress. This could potentially result from better analytic techniques.

Allostatic load measures have highly variable time frames. Some may change relatively quickly, e.g., fibrinogen, some are integrated over some time period (e.g., 12-hour urinary cortisol), and some change much more slowly or are integrated over longer time frames (e.g., waist-hip ratio or HgbA1c). Most physiological parameters are not only stress indicators but also change with other biorhythms, e.g., circadian or prandial.

Another rationale for allostatic load as a composite measure of stress effects is that different people likely have different subsystems affected by stress. Some people experiencing high stress develop headaches, while others develop gastrointestinal or other disorders. The particular organ systems affected by stress is an interaction between these systems and the brain. The individual reactions to stress are dependent on an individual's genes, learning and environment. Thus, it is likely that different people have different patterns of alteration in stress-related biomarkers or allostatic load component measures that may potentially be discerned by better analytic techniques, e.g., structural equation modeling or machine learning. It may ultimately be important to understand the individual relationships, but at this state of the research it may be helpful to have a combined measure.

4.4. Stress and disease

Acute stress may have some metabolic, immunologic and cognitive benefits. For example, alterations in system properties may produce a higher transient utility, decrease the likelihood that a stressor will move the state of the system away from an optimal attractor (robustness), or increase the size of an attractor basin (see hormesis below). A helpful example is the immune system which learns to react to foreign substances when exposed to non-virulent ones that do not result in death. If the immune system is not exposed to sufficient foreign substances,

the result could be over-reactivity to foreign substances or allergies [184].

However, as stated in the introduction, more often impairments in health and a broad range of diseases are produced by chronic psychological stress.

Chronic stress may cause cognitive decline, adverse effects in the hippocampus, and contribute to neurodegenerative diseases either directly or through stress mediators including allostatic load [24, 25, 27, 117, 185]. The negative effect of psychological stress on cognitive function may be greater with aging [28-30].

Stressors including anesthesia, drugs, depression may be more likely to result in a state of impaired cognitive function with increased age. Cognitive reserve, a measure of how well the brain works [52], may be one aspect of resilience to the effects of stress on cognition.

5. Dynamics of stress system - time course of stress-induced physiological changes: state/trait and variables/parameters (Figure 2.4)

Stress can cause a perturbation of state but the associated changes to physiological measures occur at varying time scales. The time courses of marker changes in psychology are sometimes grouped into fairly mobile, shorter-term changes reflecting the person's current *state* and longer-term, more stable changes reflecting *traits*. Standard measures of psychological stress aspects, such as anxiety, are often measured by a widely used inventory, e.g. the State-

Trait Anxiety Inventory [186]. However, even relatively stable traits, such as the personality trait neuroticism, often considered stable over a lifespan, can be malleable thus limiting the clear distinction between state and trait. Systems science uses terms analogous to state and trait: *variables* reflecting current state measures and *parameters* reflecting more stable attributes of the system. The change in parameters may decrease the likelihood of the system staying in the optimal attractor basin in the face of typical environmental fluctuations, but the distinction from variables is simply the time scale and thus is somewhat artificial. This section is focused on the varying time courses of physiological markers which are only moderately correlated with commonly used self-rated markers. All biomarker measurements, including common physiological measurements (e.g., cortisol) and many anatomic and experimental physiological measurements (e.g., hippocampal size or neuronal receptor sensitivity) change over time, but the time courses differ.

The sympathetic branch of the ANS is the quickest to respond. Stress response can be measured by heart rate, blood pressure, electrodermal activity, or catecholamine release [187]. Epinephrine and norepinephrine release occur in seconds. The two-minute half-life of epinephrine highlights the generally short time course of this response. This ANS response is presumably geared to short-acting flight-or-fight changes such as metabolic needs, blood flow, and non-specific alerting of the brain [188], with norepinephrine projecting throughout the

brain contributing to both phasic and tonic alertness [189, 190]. HPA activity has a slower time course and is activated by threats and negative consequences even when only anticipated. Cortisol has effects throughout the body and is impacted by many factors other than stress. Cortisol also directly affects the brain via cortisol receptors present in the pituitary, cerebellum, hypothalamus paraventricular nucleus and in neocortex. The cortisol peak onset occurs 15-30 minutes after a stressor [178, 191].

Stressor effects on the immune system have a long-time course, and effects on learning and DNA have even a longer-time frame and are important for sustained stress effects. Some personality traits have been linked to specific genotypes, e.g., single nucleotide polymorphisms. For example, a specific genotype (5HTTLPR) relevant for stress affects serotonin transport and has been related to stress reactivity [192] and the personality trait of neuroticism. Particularly relevant for our discussion involving time courses in human stress are the brain network changes altering perception of the stressfulness of an environmental stimulus; this may be related to sudden awareness (consciousness) of the stressor or of the induced physiological state change. A system that reacts differently if consciousness is achieved and responds based on conscious perceptions and concepts, such as the perception of causality, is inherently biased.

There are different approaches to measure stress and resilience dynamically. One can measure the magnitude of the change at some time point following a stressor, e.g., the cortisol increase from baseline to 15 minutes after an experimental stressor. One can incorporate a more sophisticated temporal measure estimating the area under the curve or half-life of a biomarker stress response if enough assessments are available. Another measure is the time it takes to return to baseline following an experimental stressor, e.g., fMRI changes 2 hours after a stressor [63]. In the event one does not use an experimental stressor, one can observe response following a significant environmental stressor, as in epidemiological studies related to war injuries or catastrophes. If enough measurements over sufficient number of days are available it is possible to calculate the variability of the physiological system. This variability of the system relates to stress responses but other variables (e.g. age) enter as well. For example, aging is associated with increased variability of measures of performance, and this variability can serve as a marker for insipient dementia among elders [193].

In general, the slowly changing traits or parameters are potentially harder if not impossible to measure empirically. Given the variable time frame of the biomarkers, assessment by many repeated measurements over a prolonged period may provide a better representation of the dynamical stress system response to psychological stress than single time-point assessments. This is

especially true because each biomarker already captures the physiological system over some cumulative time window. The many physiological measurements needed over a prolonged time can be obtained over days or weeks using continuous recording in a lab or repeated assessments using ecological momentary assessment [194, 195]. Looking at reactivity to an experimental laboratory stressor may also provide good markers of the dynamic nature of the physiological system related to stress. Epidemiological studies can use data acquired following population exposure to a common stressor. Figure 2.4 offers a schematic representation of the conditions related to shorter- and longer-term stressors and physiological responses. There are many systems science methodologies that could be used to analyze the multidimensional nature of stress physiology including system dynamics modeling, agent-based modeling, network analysis, discrete event analysis, Markov modeling, and control systems engineering [119].

6. Resilience

As discussed in the introduction, the term *resilience* has been used in different ways. *Resilience* affects how effectively and quickly the system returns to a high utility attractor basin [44]. Despite the neuroscientific interest in resilience [45, 57], its definitions remain variable. *Resilience* or *robustness* is the capacity of the system to return to a high utility attractor following perturbation, the system's ability to avoid shifting to another attractor basin presented in this paper as a

dysfunctional or diseased condition, or moving more quickly to its optimal location within its original attractor basin (Figure 2.1). Specific examples of resilience from a systems perspective include: 1) the distance of a location in one attractor basin to the boundary of an adjacent basin of inferior utility, i.e., greater resilience means the attractor is further away from boundaries with low utility neighboring regions; and 2) the strength of the vector field in the basin, where resilience might mean more rapid return to the attractor, so a repeat of a state perturbation before full return will make leaving the basin less likely. From a biological perspective, *resilience* may refer simply to the ability of a person to cope with a significant external stressor or insult. Related terms include: *stability* or *resistance*, indicating the difficulty moving a system away from its baseline "optimal" region; *precariousness* suggesting system proximity to some threshold of moving into another attractor basin, and *latitude* related to the maximum amount of change the system undergoes before losing its ability to remain within its high utility attractor basin. The resilience of a dynamical system to maintain itself within a functional high utility attractor basin is very important to the long-term health of the system. Resilience is not simply the opposite of allostatic load. Allostatic load is a measure of physiological system parameters that may impact resilience but it also has other effects on long-term health or disease risk.

It is known that many human stressors are best remediated by significant behavior change affecting stressor exposure (e.g., ingesting less glucose if pre-

diabetic or decreasing work hours in a stressful job if hypertensive); some stressors in humans are related to the perception of the stressor more than the stressor itself. For example, someone with PTSD is in a pathological lower utility attractor that could relate to the brain misperceiving the environment in a way harmful to the person's health (e.g., a truck backfire causing a veteran to engage in recollections and emotions associated with war).

Resilience to psychological stress is evident when some people avoid significant psychopathology, such as PTSD and depression when exposed to a stressor [45]. In the World Trade Center disaster resilience, measured by a likelihood of developing PTSD, was related to age (older did better), gender (males did better), social support (more did better), self-esteem (higher did better) and lifetime history of depression (worse with a positive history), but was not related to education [47].

Some amount of stress in the environment may be useful for maximizing the system's ability to respond to future stressors. Humans living with no stressors may lose the ability to respond to future stressors. From the brain perspective, some amount of stress is useful for maximizing learning and maintaining cognitive function. Systems that learn to cope with some amount of stress may be less affected by future stressors. *Hormesis* refers to a biphasic response to a

stressor, "a process in which exposure to a low dose of an environmental factor that is damaging at higher doses induces an adaptive beneficial effect on the cell or organism" [65]. This adaptation could be to environmental stressors such as cold and exercise [66]. A stressor can cause the system to be non-optimal for a short time but still result in returning to baseline. While there may be some allostatic load cost, the stressor may induce changes in system physiological parameters that strengthen the future ability to return to its greater utility locations, i.e., increase resilience. This low level of stress exposure occurs in some clinical treatments, e.g., allergy therapy and exposure therapy in PTSD. In some sense such exposures to a low-level stressor is a way to exercise the resilience aspects of the system. In general, repeated external stimuli elicit less of a physiological response because of habituation that can be measured by fMRI, event-related potentials or electrodermal response [196, 197]. However, in some cases repeated external stressors result in the excessive response, as in PTSD (e.g., hyperarousal to loud noises) and become self-reinforced rather than extinguished.

This decreased efficiency and ability of the human dynamical physiological system to stay in or get back to a functionally positive attractor basin is the negative effect of chronic stress or allostatic load. Changing the parameters of the human system to bring the system back to the optimal state or high utility attractor often entails a cost to the basic human constituents but the changes can

be used to simply indicate previous stress exposure. This could be DNA modification, receptor sensitivity changes, or changes to blood vessels from high blood pressure. Another example of changes to the underlying system is aging, which can make a person more likely to exist in a non-optimal state or attractor basin. It could be that the attractor basin becomes smaller or less steep. The change of the state space attractor basin that decreases the system's ability to stay in its higher utility states without moving to lower utility states in its current attractor basin or to a lower average utility attractor basin represents the chronic stress effect or allostatic load. These changes over time can be defined mathematically. The suboptimal attractor basins do not become necessarily larger; rather, the high utility attractors become smaller with shallower sides. Thus, the time required for return to the baseline state tends to increase.

From a probabilistic perspective, the resilience of the system could be considered the probability that an environmental perturbation results in returning to the high utility attractor basin, as opposed to ending up in an attractor basin with lower utility. The capacity of a system to stay in a high utility attractor basin could be defined stochastically: the likelihood that following a particular perturbation the person returns to the high utility attractor basin. The capacity to stay in this high utility attractor basin is especially relevant when, following a stressor, the state may be closer to the basin boundary and be more likely to shift to a non-optimal attractor basin should another stressor manifest. Even without

changing the specific attractor basin but simply the shape of the basin, resilience could be defined based on the probabilistically weighted average utility in a single attractor basin following expected stressors.

PTSD is a useful example of state space and attractors since some of the physiologic responses may initially have been an adaptive response during specific time and environment but when they persist in other environments, the result is moving to a lower utility attractor where the abnormal response is self-reinforcing. A high stress physiological state may be high utility during a war but if that state persists after returning home it can be lower utility. The transition to PTSD is not reversed immediately as soon as causes are reversed or disappear. Reversal might require going all the way back to an earlier state in a system which induces the possibility for a cusp catastrophe (Figure 2.2).

7. Environment and its perception

In addition to knowing the physiological state of the person, one should also know the state of their environment because certain physiological measures may be a reaction to the environment. It must be reiterated that although some environmental stressors have a direct effect on stress responses, e.g., extreme cold, stress responses are significantly related to the person's perception of the stressor. The perception of the environment (Figure 2.3) is affected by a person's

prior experiences through attention and memory. Many environmental stressors are stressful because of the way they are perceived and processed. A person focused on an important phone call may not realize it's hailing outside because of their attention on call. As a result, one may not be worrying about whether the car was left outside the garage. Attention refers to systems in the brain that allow some information to be processed more than other information [198]. Memory is a broad term with many subsystems loosely divided into declarative and non-declarative memory [199]. Emotional memory has critical brain hubs not relevant for other types of memory. The amygdala rather than the hippocampus is critical for registering the emotional valence of an event [200]. Beta-blockers that block aspects of the ANS can have an impact on emotional memory without any impact on episodic memory [200, 201]. The memory-induced changes in neural connectivity that result from gene expression and protein synthesis require hours to days. A person with a memory of a previous environmental stressor will perceive the perturbation differently from the person with no prior associations to it. For example, a physically abused wife might associate the noise of her husband returning home with the physical abuse that often follows. The sound of an opening door will have different neural associations to her than her non-abused neighbor.

High reactivity to negative events produces physiological changes [32]. In fact, negative reactions to events are more predictive of emotional well-being than the

event itself [33]. Reactivity to stress can be examined through neuroticism, one of the five factors in the widely used five-factor personality inventory [202].

Neuroticism has genetic, neurobiological, and environmental contributions [30, 34, 35]. High neuroticism contributes to many health disorders [36] and relates to increased age-related cognitive change and clinical Alzheimer's disease in longitudinal studies [37-39]. The cognitive deficits related to distress proneness are not specific and most consistently included frontal-executive function and perceptual speed [37, 39], not dissimilar to cognitive changes associated with affective disorders such as PTSD and depression [40, 41]. Neuroticism with its negative effects on cognition is a modifiable risk factor [42] with a potentially large impact on population health [43].

The internal physical components of the human are part of the brain environment, considered the internal environment in contrast to the external environment located outside the physical body. The brain has partial awareness of the internal (interoception) and external (exteroception) environment. Interoception and exteroception may produce brain and other physiological changes without awareness, but humans can become aware of their internal states such as anxiety or stress. Interoception may be taught as awareness and control over internal organs (e.g., learning to modulate one's blood pressure through biofeedback or mind-body practices).

As previously mentioned, the effect of an environmental stressor on health may be modified by how the brain perceives the environment. This perception can be altered by higher level concepts beyond attention and memory as highlighted by the concept of hope. From a health perspective, optimists fare better than pessimists [203] and those with higher religious involvement and spirituality do better than those with lower involvement [204]. The beneficial placebo response, i.e., the improvements in physiological measures or perceptions of health following administration of a treatment without any direct biological affect, can be elicited by merely telling someone that a treatment may work (even if there is no directly active components in the treatment) [115, 205]. It is likely that some mechanisms of placebo or expectancy effects overlap with some of the mechanisms underlying perception of stress [206]. The major stress hormone cortisol can be altered by experimental manipulation of expectancy in placebo effect studies [207, 208].

8. Stress and resiliency biomarker changes with treatment

There are physiological and genetic markers associated with improved resilience to stress-induced physiological changes [41, 209, 210], and there are also psychological tools to increase resilience, or the ability to tolerate stress perturbations without decreasing utility. Exposure therapy has been used to reduce the person's reactivity to stressors, e.g., an allergen or an environmental stimulus precipitating PTSD symptoms. Mind-body techniques and biofeedback

provide cognitive strategies to decrease emotionally-activated responses, avoid unnecessary negative internal associations (i.e. sense of stress) to current events, and to maximize capacity to return to a positive state attractor following a stressor.

A key facet of many mind-body therapies is mindfulness, attending to the present moment in a non-judgmental way. With several ways to measure mindfulness, the judging and negative appraisal of thoughts, emotions, and behavior factor may be particularly important for stress management. The mindfulness-non-judgmental score, i.e., being aware of the environment without attaching an emotional tag [88], is diminished by the chronic stress in dementia caregivers and in veterans with post-traumatic stress disorder [30, 211].

Mind-body studies have suggested biomarker changes related to mindfulness or mindfulness training partially overlap with the allostatic load biomarkers but in the opposite direction. These include telomerase[212], immune function [213, 214], cognitive function [214, 215], catecholamines [216], HRV [217], cortisol [214, 218-220], EEG [112], structural MRI [221, 222] and fMRI [223]. Meditation alters physiological responses to an experimental stressor [93]. However, the preferred or composite biomarkers relating to benefits of mind-body medicine have not been identified.

9. Utility

Utility is essentially the same as success of the organism (e.g., life, procreation or, in the case of humans, earning money). Long-term health is an important focus of the utility definition concerning stress-related impact on human health. While utility is the benefit to the person (or genes), the benefit also depends on the environment, i.e., the specific calculation of utility varies with the environment and the time course over which it is calculated. During war, utility is more immediate, perhaps simply surviving to the next day with a very high discount for future situations. Therefore, utility of a response to a stressor depends on the environment and on a person's degree of discounting future events. Thus, the calculation of utility in different environments will be dependent on the rewards and penalties in the current environment and on the time duration and differential weighting used for calculating the utility.

10. Conclusions

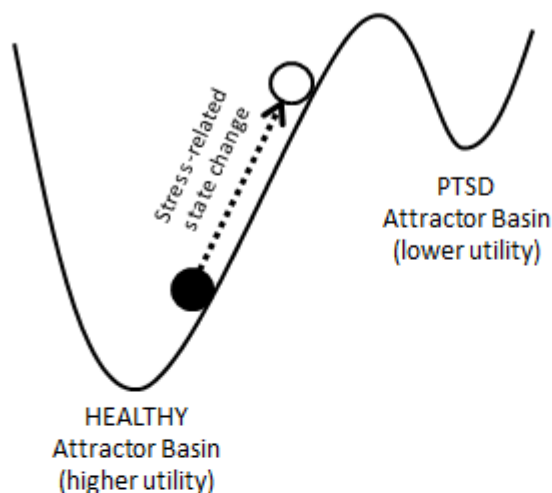
This paper has described human stress physiology and psychology from the systems science perspective. Specifically we focused on environmental perturbation stressors that produce significant long-term changes in the human dynamical system. Acute stressors usually do not produce long-term negative effects although a significantly powerful acute stressor may push the brain

dynamical system into a new, functional attractor basin with lower utility. In general, chronic psychological stress produces changes in the system, such as a slower response to a future stressor or a higher potential for moving to a new lower utility attractor basin. If a human is exposed to a “tolerable” dose of a stressor that results in return to the original high utility attractor basin, the outcome may be improved resilience. From a systems science perspective, behavioral and physiological measurements attempting to capture the degree of stress of a system should incorporate the dynamics of the physiological stress response system as well as some measures of the environmental stressors and their perception. Understanding stress will require all of the interacting components from Figure 2.3 to be measured and described, at least partially. In general, the systems dynamics of stress physiology has much less temporal empirical data to inform the model than, for example, meteorological data because of the difficulty acquiring the human data. Nevertheless, analyzing dynamical data will be important to better understand stress physiology since the timing and strength of feedback loops likely contributes to disorders of stress and resilience to stress. In addition to measuring stress responses over time, it may be useful to repeat administration of experimental stressors to understand self-reinforcing loops. These systems science concepts and better measurement techniques will lead to better understanding of the stress system that ultimately can be used to improve the resilience of the human system and thereby improve long-term health.

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a) Higher Resilience Case



b) Lower Resilience Case

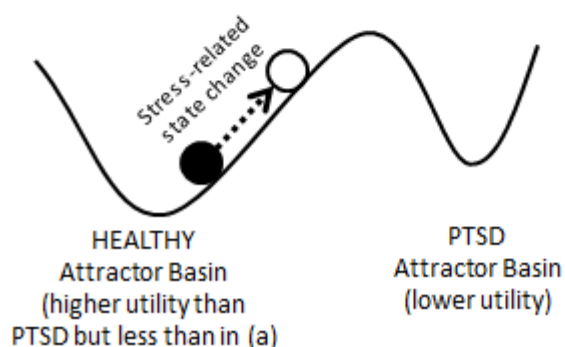


Figure 2.1. Schematic of attractor basins for high and low resilience.

Hypothetical example of space of possible human physiological states with two attractor basins, one being a healthy higher utility condition and one a lower utility condition state of PTSD (in this figure, higher utility is downward). The attractor basins can tolerate movement of the hypothetical person (solid circle) in the horizontal direction from an external stressor without leaving its basin of

attraction. However, with sufficient movement from a stressor, one may go from a higher utility healthy condition basin to a lower utility PTSD basin. The healthy condition in b has lower resilience than in a, with less stress required to shift it to the lower utility basin.

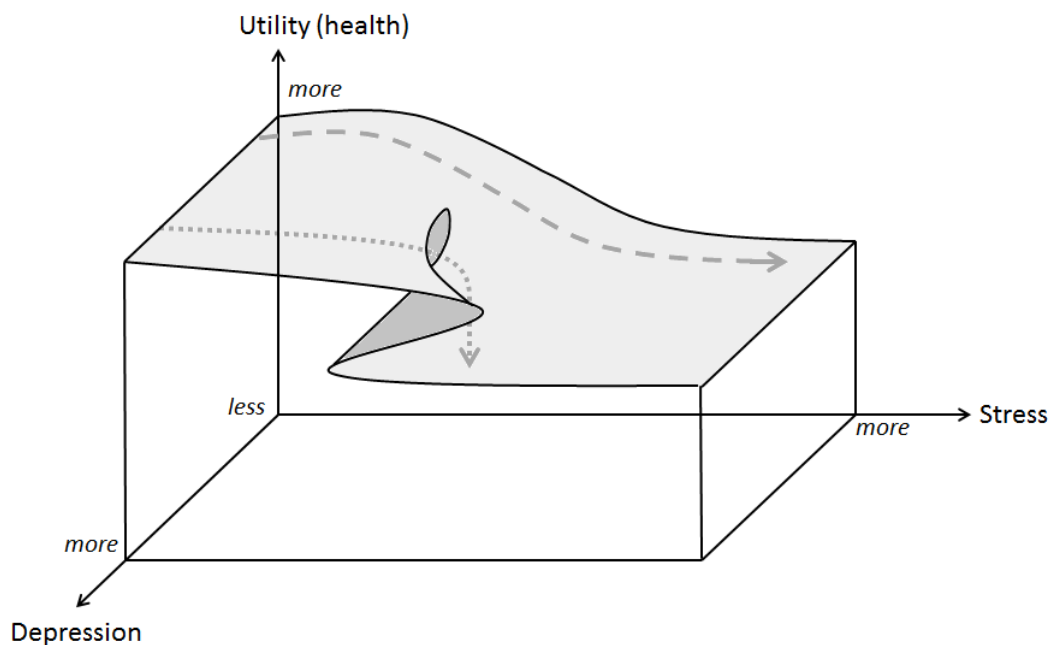


Figure 2.2. Schematic of cusp catastrophe for post-traumatic stress disorder. An example of a cusp catastrophe where the state space of human physiology has a complex 3-dimensional shape, with no pictorial representation of attractors, and there may be an abrupt state change. In this example, as stress increases at higher levels of depression there may be a sudden drop in location to a new state, PTSD (marked by a dotted line). Here, utility is up rather than down as in Figure 2.1

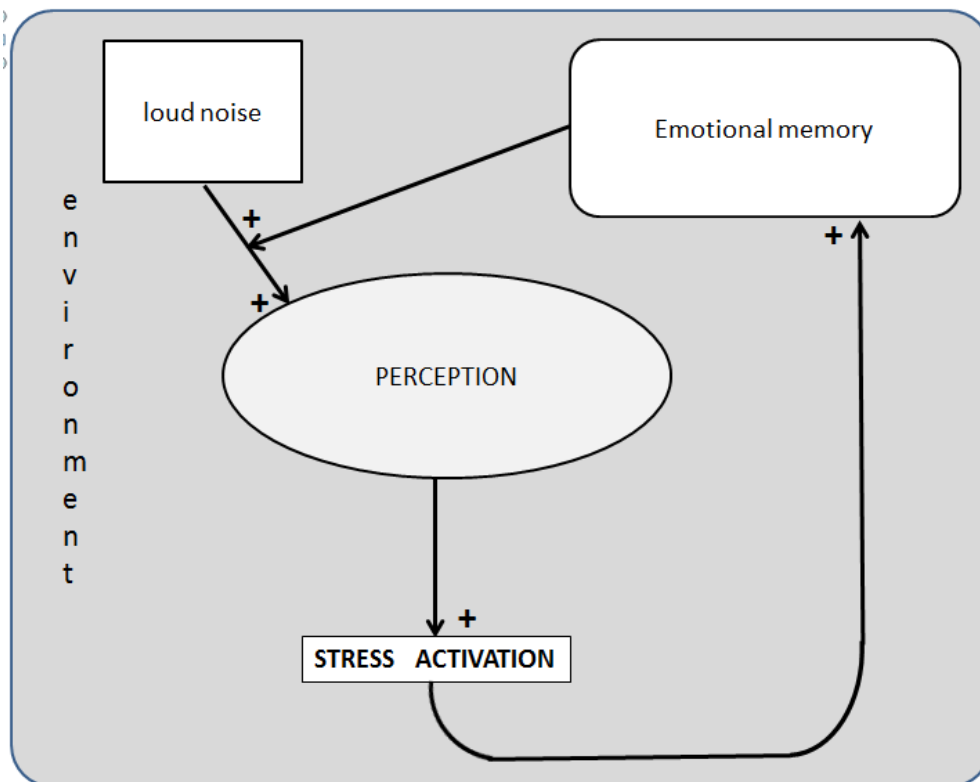
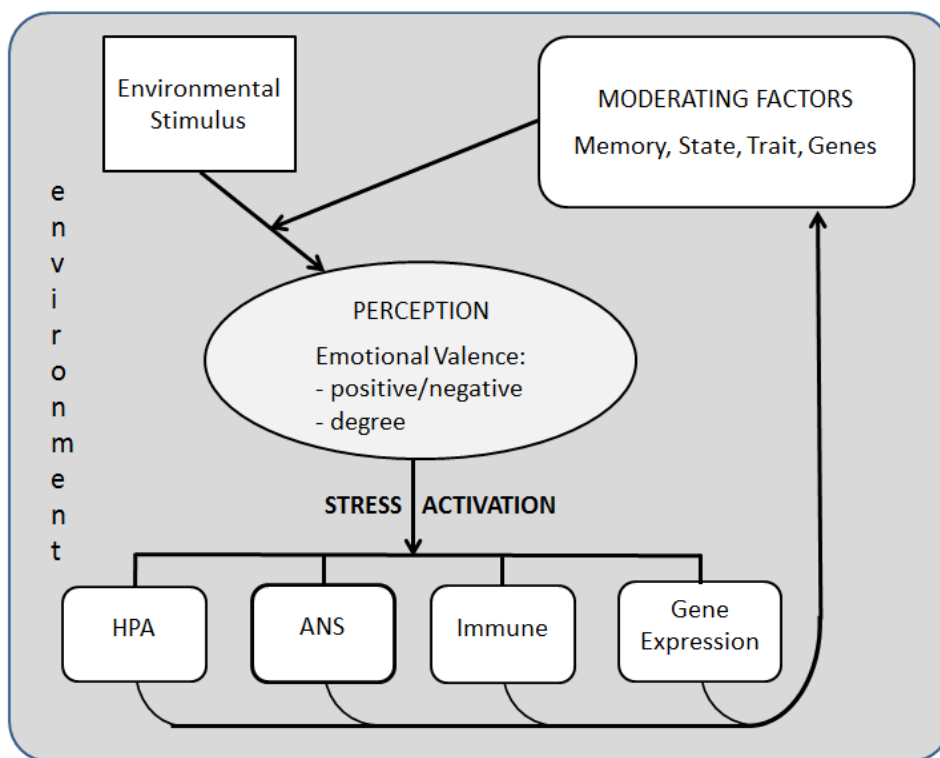
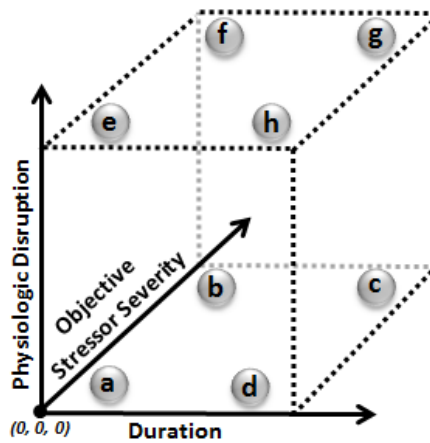


Figure 2.3. Stress system with input, brain, effectors, and moderators

(2.3 Top) The brain's perception of the emotional valence of an external event as a stressor is dependent on the current environment and modulated by previous experiences (memory), current physiological state, traits (e.g., neuroticism), and genotype. The brain generates outputs to the autonomic nervous systems (ANS), the hypothalamo-pituitary-adrenal (HPA) axis, the immune system, gene expression and epigenetics (overall increasing time duration of stress activation components from left to right). These responses directly affect the body but also feedback to the brain. Learning includes assessment of risks and rewards and it can be clinically designed to reduce reactivity, e.g., allergy therapy or mindfulness meditation. (2.3. Below). Example of self-reinforcing stress response system that is pathological if in a non-threatening environment. Normally, while stress activation from a loud non-threatening noise may initially activate a stress response, response to repeated loud noise will be attenuated through negative feedback (e.g., habituation). In PTSD emotional memories and the stress activation itself may contribute to an auto-reinforcing positive feedback loop. As mentioned in the text and Figure 2.2, this PTSD attractor basin may be entered secondary to a single severe negative event via a catastrophic dynamical systems event. This pathological transition is more likely in those with predispositions, e.g., neurotransmitter alterations such as depression.



STATE EXAMPLES

- a. Relaxation
- b. Inappropriately low response due to inattention, trait, etc.
- c. Diminished response to chronic stress
- d. Boredom/lack of stimulation
- e. Exaggerated transient response
- f. Normal transient stress response
- g. Hyperarousal/sensitization to chronic stressor
- h. Exaggerated chronic response

Figure 2.4. Potential state examples based on 3-dimensional stress model

A rough schematic of three dimensions related to stress. Physiological activation can be low or high and sustained for a short or long period of time. The response can be to a stressor that is relatively low from an objective or population perspective or relatively high. Normal function usually goes from relaxation state (a) to short duration high physiological activation when exposed to a stressor (f). If the stressor response is too sustained or occurs too frequently, there is some cost to the system.

Chapter 3.

Meditation in stressed older adults: effects on stress, affect, cognition, and physiology.

(edited version submitted to Psychology and Aging, January 2016)

Abstract

Objective: Determine if mindfulness meditation (MM) in older adults will improve measures of psychology, cognition and physiology impacted by stress.

Methods: 134 at least mildly stressed 50-85 year olds were randomized to a six-week one-on-one MM intervention along with home practice or to a wait-list control (ClinicalTrials.gov NCT01386060). Outcome measures assessed at baseline and two months later at Visit 2 included Positive and Negative Affect Schedule (PANAS), Center for Epidemiologic Studies Depression (CESD), Perceived Stress Scale (PSS), Neuroticism-Extraversion-Openness (NEO) personality traits, SF-36 health-related quality of life, a broad cognitive function battery with emphasis on attention and executive function, salivary cortisol, respiratory rate, and heart rate variability.

Results: 128 participants completed the MM study though Visit 2 assessments. Self-rated measures related to negative affect and stress were all very significantly improved as a result of the MM intervention (PANAS-negative, CESD, PSS, and SF-36 health related quality of life (Vitality and Mental Health Component)). There were significant changes in some personality traits especially Neuroticism. Positive affect were not significantly changed. There were no changes in cognition, salivary cortisol, and heart rate variability.

Conclusion. Mental health in the MM intervention group was significantly improved compared to the wait-list control, with some clinically important differences in SF-36 Vitality and Mental Health Component scores. These self-rated improvements were not paralleled by improvements in cognitive function or physiological measures. Potential explanations for this discrepancy in stress-related outcomes are discussed at length.

Keywords (up to six)

Meditation, stress, cognition, fatigue, mental health, older adults

Abbreviations/acronyms

BP – Blood Pressure

CAR – cortisol awakening response

CERAD – Consortium to Establish a Registry for Alzheimer’s Disease

GDS – Geriatric Depression Scale

GPSE – General Perceived Self-Efficacy

HRV – Heart Rate Variability

LF/HF – Low to high frequency

PTSD – Post traumatic stress disorder

PSS – Perceived Stress Scale

CESD – Center for Epidemiologic Studies Depression

PANAS – Positive and negative affect schedule

PSQI – Pittsburgh Sleep Quality Inventory

NEO – Neuroticism-Extraversion-Openness

SF-36 – Short form 36-item health related quality of life

FDR – False discovery rate

MM – mindfulness meditation

Resp - Respiration

SDRR – Standard deviation of inter-beat interval

WAIS- Weschler Adult Intelligence Scale

Currently, age-related cognitive decline stands as a major public health issue, with high societal costs and few preventative options. The prevalence of cognitive decline associated with functional impairment, referred to as dementia, is about 14% of Americans over 71 years old [1] with a resultant high cost to the US of \$200 billion [2]. Cognitive impairment without dementia in those over 71 is even more prevalent, affecting about 22% of the population [3]. Older adults are more likely to develop cognitive symptoms from medical conditions. For example, in addition to slow progressive cognitive decline, older adults are much more likely to develop significant, transient cognitive impairments, even to the point of delirium. A weakening of overall brain function could be caused by depression, nutritional deficits, oral medications with central nervous system effects, anesthetics, or simple hospitalization [6-8]. This point highlights how older adults are more susceptible than younger adults to any process that negatively affects brain function. Despite the personal and societal costs and known epidemiological risk factors, such as hypertension and low education, there are no evidence-based recommendations for prevention of age-related cognitive decline [4]. Mildly improving cognition and delaying the onset of dementia by even 6 months with a widely available behavioral intervention would decrease the number of dementia cases by over 100,000 over 10 years [5]. Developing evidence-based strategies to decrease the negative impact of depression and stress that contribute to age-related cognitive decline was one goal of this study.

Psychological stress is one important factor in the general population and specifically with older adults that can be addressed by behavioral interventions. Psychological stress is very common and contributes to many physical and mental health problems. About 25% of surveyed American adults reported high stress and 50% reported a major stressful event over the past year [9]. Stress is potentially caused by events with **N**ovelty, **U**nexpectedness, **T**hreat to ego, or **S**ense of not being in control (NUTS) [10]. Chronic psychological stress has multiple effects on physiological systems [24, 224] and the underlying pathophysiology of stress-related symptoms, contributing to a broad range of diseases, such as cardiovascular health [11-14], epilepsy [15], Parkinson's disease [16-18], multiple sclerosis [19, 20], eating disorders, and addictions [21]. Stress may also worsen behavioral symptoms, such as anger and anxiety, which symptomatically worsen disorders such as traumatic brain injury, post-traumatic stress disorder (PTSD), and dementia. Importantly, chronic psychological stress and excessive reactivity to stressors contributes to age-related cognitive decline, hippocampal injury, and neurodegenerative diseases either directly or through stress mediators [14, 22-27] with the effect being even greater with aging [28-31]. Higher reactivity to negative events produces physiological changes [32]. In fact, negative reactions to events are more predictive of emotional well-being than the event itself [33]. Elevated stress reactivity associated with negative emotions, neuroticism, has genetic, neurobiological, and environmental contributions [30, 34, 35]. High neuroticism contributes to many health disorders [36] and is linked

to increased age-related cognitive change and clinical Alzheimer's disease in longitudinal studies (although the neuropathology of this cognitive change or clinical dementia syndrome is not related to amyloid deposition) [37-39].

Proneness to distress elicits deficits that are not specific and consistently include frontal-executive function and perceptual speed [37, 39], similar to cognitive changes associated with affective disorders such as PTSD and depression [40, 41]. Reducing stress reactivity and thus its negative effects on cognition may be a modifiable risk factor with a potentially large impact on population health [43].

Mindfulness meditation (MM) is a behavioral intervention that shows promise in being able to reduce stress and stress reactivity in many health conditions. MM is a popular meditation approach that has been formally studied and applied in a variety of clinical conditions including PTSD, depression, pain, and stress [75-83]. However, the evidence for efficacy has not been definitive across the board in part related to lack of objective not self-rated markers of improvement [84-86, 225] although there is moderate evidence for the reduction of anxiety, depression and pain symptoms [86, 87, 225]. Mindfulness meditation has not been well evaluated in older adults as a behavioral intervention to reduce stress and stress reactivity and thus, potentially improve cognitive function.

Goals of study

The goal of this study was to further elucidate and better define the benefits of

MM training in older adults using a broad battery of outcomes related to stress, physiology, and cognition. This goal was accomplished by examining which outcomes have greater effect sizes from MM training. In a randomized controlled trial, mildly stressed older adults were allocated to a six-week one-on-one MM intervention or a wait list control. We hypothesized that psychological, cognitive and physiological measures related to stress would improve with the MM intervention.

METHODS

Participants

Participants consisted of generally healthy adults 50-85 years of age who reported at least mild levels of stress. The upper age cutoff helped to limit instances of multiple brain pathologies contributing to age-related cognitive alterations [55, 226, 227]. Participants were recruited from the Portland, Oregon metropolitan area.

Following inquiries, participants were informed about the study and eligibility criteria. If interested, they underwent a 30-minute telephone eligibility screening for which there was an IRB-approved Waiver of Authorization granted where health history and demographic data were collected and several questionnaires were administered. This study was approved by the Oregon Health & Sciences University Institutional Review Board (IRB) and was registered with

ClinicalTrials.gov (NCT01386060). Participants provided informed consent during Visit 1 at the research lab. Exclusion criteria were primarily to screen out an underlying illness that might limit the benefit of the intervention, confound outcomes, or increase the likelihood of dropout (Table 3.1).

Table 3.1: Inclusion and exclusion criteria

Inclusion Criteria	<ul style="list-style-type: none"> • Age 50-85 years old; • Baseline Perceived Stress Scale (PSS) [228] score ≥ 9; • Agree to follow the study protocol including randomization
Exclusion Criteria	<ul style="list-style-type: none"> • Cognitive impairment (significant participant complaints) or a score of less < 30 on the Modified Telephone Interview for Cognitive Status (TICS-m) [229] • Significant patient-reported medical/neurologic disease (e.g., major organ failure; insulin-dependent diabetes, active cancer, or alcoholism); • Significant, untreated depression. Significant was defined based on Geriatric Depression Scale greater than 5 and interview; • Take medications known to affect CNS function or impact physiologic measures (e.g., steroids, neuroleptics or regular narcotic analgesics); stable doses of CNS-active drugs with less impact (e.g., beta-blockers, SSRI's, and histamine blockers) were acceptable; enrolled participants were encouraged not to change their drug use during the study period and to inform the investigator if any change was made. • Cannot understand the instructions (e.g., cannot hear or see study materials or not fluent in English); • Prior experience with meditation classes or other mind-body classes (e.g., yoga or tai chi) within the last 24 months or more than 5 minutes daily practice in the last 30 days.

Randomization and follow up

Following Visit 1, participants were randomized to a six-week one-on-one MM intervention or a wait list control. All randomizations were performed by non-blinded research personnel using a computerized covariate adaptive randomization procedure [230] aimed at balancing active and wait-list groups on age, gender, and baseline Perceived Stress Scale score using a pre-determined projected median split for the continuous measures. The research assistant who led the meditation training sessions performed the randomization, and the research assistants who conducted data-collection visits remained blinded. There were three assessment visits that were approximately three hours long and two months apart. Participants in the MM group received a 6-week one-on-one intervention adapted from MBCT [231] between Visits 1 and 2 but received no intervention between visit 2 and visit 3. In contrast, participants in the wait list group received no intervention between visits 1 and 2, but received the 6-week one-on-one intervention between visits 2 and 3. This primary outcome paper analyzes only the Visit 1 and Visit 2 data. The outcome measures include: 1) self-rated measures of stress and affect and 2) biomarkers of stress including cognitive function, salivary cortisol, blood pressure, respiration rate, heart rate and heart rate variability (HRV).

Intervention

MM was the active intervention administered in this randomized controlled trial

(RCT). The intervention was administered in six, one-on-one training sessions occurring weekly and also involved recommended daily home-practice. As mentioned above, an unblinded research assistant delivered the training sessions.

MM: The MM in this study is a standardized and structured one-on-one program [231] based on MBCT [232, 233]. The MM training objectives were to: 1) help participants understand their personal reactions to stress, 2) teach those skills to modify their stress reactions, and 3) promote their desire for self-care and feelings of competence and mastery. Participants attended 60-90 minute training sessions once a week for six weeks, and the six trainings all followed a similar format. The length of the sessions varied to some degree by weekly syllabus length and by participant characteristics. Most sessions began with a 30-minute guided meditation, followed by discussion about the participant's meditation experience, conversation about establishing a regular home practice, presentation of new materials, and explanation of home practice. Formal meditation instruction included a 30-minute Body Scan, 30-minute Sitting Meditation, 30-minute Sitting with Difficulty Meditation, and 4-minute Breathing Space. Informal practice of mindful daily activities (e.g., washing dishes, eating) were taught to generalize mindfulness beyond the formal meditations. A brief 3-Step Coping Space meditation was also taught as a quick coping strategy intended to be used during times of stress in daily living. The research assistant leading the MM intervention was educated in Buddhist meditation with previous

experience teaching secular 1-on-1 MM with adults enrolled in other RCTs [234, 235].

Participants were instructed to practice at home 30-45 minutes a day as a goal but to practice at least some amount every day. The meditation home practice audio recordings had several possible shorter interval breaking points denoted by tones to allow flexibility for unpredictable time demands facing stressed adults. MM sessions will also offer strategies other than meditation for practicing mindfulness skills to cope with the many stressors that adults typically face.

Wait-list: Participants randomized to the wait-list arm between Visit 1 and Visit 2 received the MM intervention after the wait-list period (i.e., between Visit 2 and Visit 3). This was done in part to facilitate recruitment and decrease disappointment following randomization.

Adherence (Compliance) and retention: Attendance at the weekly in-person sessions was tracked. Adherence to the MM home practice for the MM intervention was assessed by iMINDr, a software application on a study iPod Touch (Apple, Inc.) lent to the participants for the duration of the study [116]. All participants met with the non-blinded RA six times for 90 minutes during the active 2-month intervention block.

Outcomes

The outcomes were self-rated questionnaires, cognitive assessments, and physiological measures.

Self-rated measures (Stress, affect, personality and quality of life

outcomes). At all outcome visits, participants were assessed with self-rated measures that might be affected by the MM intervention or mediate the MM intervention effect on the objective measures. Forms were sent to participants prior to the in-lab assessment visits and were filled out at home, taking less than one hour to complete.

- Stress: Perceived Stress Scale [228].
- Personality: While neuroticism has been considered a stable trait, changes in neuroticism are a possible outcome from meditation studies [212]. Neuroticism was assessed with the shortened version of the NEO [202] that assessed the other personality traits as well.
- Affect: Positive and negative affect schedule (PANAS) [236] and the Center for Epidemiologic Studies Depression Scale (CESD) [237]. While the conventional, standard, 20-question trait version of the PANAS was filled out at home, the 10-question state-version was filled out in the lab setting [236, 238, 239] in preparation for its use in ecological momentary assessment. The state question PANAS asks participants “right now I feel ...?” in contrast to the standard version that asks participants “Indicate to what extent you generally feel this way, that is, how you feel on the average.”

- **Fatigue and quality of life:** The SF-36 health-related quality of life was administered. The outcome measures included the 4-question Vitality (Energy and Fatigue subscale) [240] that was previously found to be sensitive to yoga in two studies [241, 242]. Besides the Energy and Fatigue subscale, the Physical and Mental Health Composite summary scores were calculated using <http://www.sf-36.org/nbscalc/index.shtml> [243].
- **Self-efficacy:** The General Perceived Self-Efficacy (GPSE) Scale [244] was included because participants have previously reported that their sense of control was significantly affected by meditation [107, 245, 246].
- **Mindfulness:** Two factors from the Five Factor Mindfulness Questionnaire [88] were assessed: the Mindful Attention Awareness Scale and factor 5, mindful non-judging. The latter was found in prior studies to be significantly different in chronically stressed populations, i.e., it was different between veterans with and without PTSD [211] and between dementia caregivers and non-caregivers [30].
- **Sleep:** The Pittsburgh Sleep Quality Index (PSQI) [247] was administered because mind-body therapies improve sleep function [248] and may mediate stress effects on cognition [249].
- **Expectancy/Credibility [250, 251] & Teacher Credibility [250, 252]** were administered to determine if expectancy is associated with any improvements observed from the MM intervention.

Cognitive assessments were based on prior studies [30, 80, 107] and focused on attentionally demanding frontal/executive function tasks but also included assessments of episodic memory and reaction time. The cognitive outcome measures were: the Stroop Color and Word Test [108, 253]; a flanker attention test where participants decide whether a central arrow surrounded by flanker arrows is pointing left or right; the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) wordlist memory test (Morris et al 1989) that is a measure of episodic verbal memory where participants are read a series of words for later recall [254]; letter and category verbal fluency from the multiple form version of the Controlled Oral Word Associates test [255]; WAIS Letter–Number Sequence that is a measure of working memory where participants are read a mixed string of letters and numbers and immediately state the string with the letters and digits each in their own alphabetic/numerical order [256] and; simple and choice reaction time [251]. The flanker attention test administered in the lab was sensitive to MM in a prior study [107] and to caregiving stress [30]. For the flanker task, to respond, participants tap on the left or right side of a touch screen on a hand-held device. The test has 30 congruent (flankers in same direction) and 30 incongruent (flankers in opposite direction) trials and lasts 2.5 minutes.

Physiological assessments were conducted at rest in the lab after participants had been seated for 30 mins and included the following: 1) systolic

and diastolic blood pressure (average of two obtained in succession using an automatic digital inflation cuff); 2) respiration rate using light elastic piezoelectric strap around chest near the diaphragm (Ambu-Sleepmate, Maryland) recorded in three consecutive 5-minute blocks when participant was listening to auditory recordings without any task and; 3) electrocardiogram (ECG) for heart rate and conventional heart rate variability (HRV) frequency analysis measures [257, 258]. Respiration was recorded during three consecutive 5-minute time blocks while the participants were seated listening to audio without any task. Respiration rate was calculated in BrainVision. Breaths were labeled semi-automatically using a voltage trigger to label peak values. HRV measures from a 5-minute recording were low frequency (LF, 0.04-0.15 Hz) to high frequency (HF, 0.15 – 0.40 Hz) ratio and standard deviation of the RR interval following methodology as used previously [153]. Electrodes were placed, amplified using BioSemi amplifiers, and ECG was processed using Kubios and BrainVision software. We also measured resting heart rate since previous findings suggested that heart rate is more sensitive to mild mental stress than the typical HRV frequency analysis measures [153]. Saliva for cortisol was collected at home and analyzed as previously done [30, 259] with saliva samples obtained on two days at three time points: immediately on awakening, 30 minutes later and before bedtime. If participants followed directions and collected all samples, data was averaged across the two days. If for any reason a sample was missing, just a single day's data were used rather than the average, knowing the single day measure might produce

significantly worse reliability [260]. Some have suggested more than two days of sampling per occasion but this study was constrained by budget to two days of sampling per visit. Thus, the cortisol outcome data for each visit consisted of a single salivary cortisol measure upon awakening, 30 minutes later, and just prior to bedtime.

Analysis

All data analyses were done in Stata 14 (StataCorp, College Station TX). Data were first inspected to ensure there were no outliers and extreme outliers (more than 4 standard deviations) were deleted. Data were assessed for normality using Shapiro-Wilk. Data transformations were used in the event of non-normality (e.g., square root or Box-Cox). Fisher's exact test was used to compare the rate of study completion.

The primary analysis for outcome measures was analysis of covariance of Visit 2 outcome data by intervention group with the Visit 1 data as covariate. Age and years of education were entered as covariates for cognitive outcome measures given their known relationship and were kept in the model if their p value was less than 0.10. There are many potential outcome measures. One goal of this study was to evaluate the MM effect sizes on all the outcome measures and these are reported as partial eta squared. For multiple comparisons, the type I rate was controlled for using the false discovery rate (FDR) [261] with an overall FDR rate of 0.05. Both the unadjusted p values and FDR corrected p values

using R program p.adjust are provided in the outcomes table but p values mentioned in the results and discussion text are all corrected values. Pairwise Pearson's correlation coefficients and unadjusted p values were calculated to better understand the relationships of the many self-rated measures.

Meditation home practice time was an important and objective measure of adherence but was only obtained in those who were randomized to receive the MM training after Visit 1. The association between meditation home practice time and outcomes was assessed using a linear regression model with the dependent variable being the Visit 2 – Visit 1 difference. In this analysis, only outcomes that were significantly affected by MM in the above ANCOVA were evaluated.

Salivary cortisol was assessed at three time points following Visit 1 and Visit 2. While multilevel mixed model analysis of cortisol data has been done previously [262, 263], we chose a simple ANCOVA analysis since there were only three data points. Outcomes were cortisol awakening response (CAR), the transient increase in cortisol for about 30 minutes after awakening, and the difference between the awakening cortisol minus the bedtime cortisol (slope). For the slope calculation, the 30 minute after awakening cortisol collection for the CAR was dropped as has been previously suggested [260, 263].

RESULTS

Following telephone screenings, 134 participants came to Visit 1 and were randomized to receive the MM beginning shortly after Visit 1 (n=66) or to wait-list control in which they received the MM beginning shortly after Visit 2 (n=68) (Figure 1). The participant demographics (Table 3.2) were mostly women as is common for mind-body studies and overwhelmingly Caucasian non-Hispanic with under-represented minority percentages comparable to Portland metropolitan area statistics for this age range. Participants were also highly educated. Only one participant was over age 75 years old. Participants were comparable in age, gender, years of education or PSS at baseline between the two groups. There were 60 participants returning to visit 2 in the MM group compared to all 68 participants in the wait-list group ($P = 0.013$).

Table 3.2. Participant demographics

<u>Variable</u>	<u>Meditation</u>	<u>Wait-list</u>
Number randomized (no. female)	66 (51)	68 (56)
Age	60.2 ± 7.4	59.4 ± 6.3
Years of Education	17.0 ± 2.5	16.4 ± 2.8
Underrepresented groups (no.)		
Hispanic	3	1
African American	1	1
Asian	2	4
Perceived Stress Scale at Visit 1	19.0 ± 6.1	18.5 ± 6.1
Return at Visit 2 (no.)	60	68

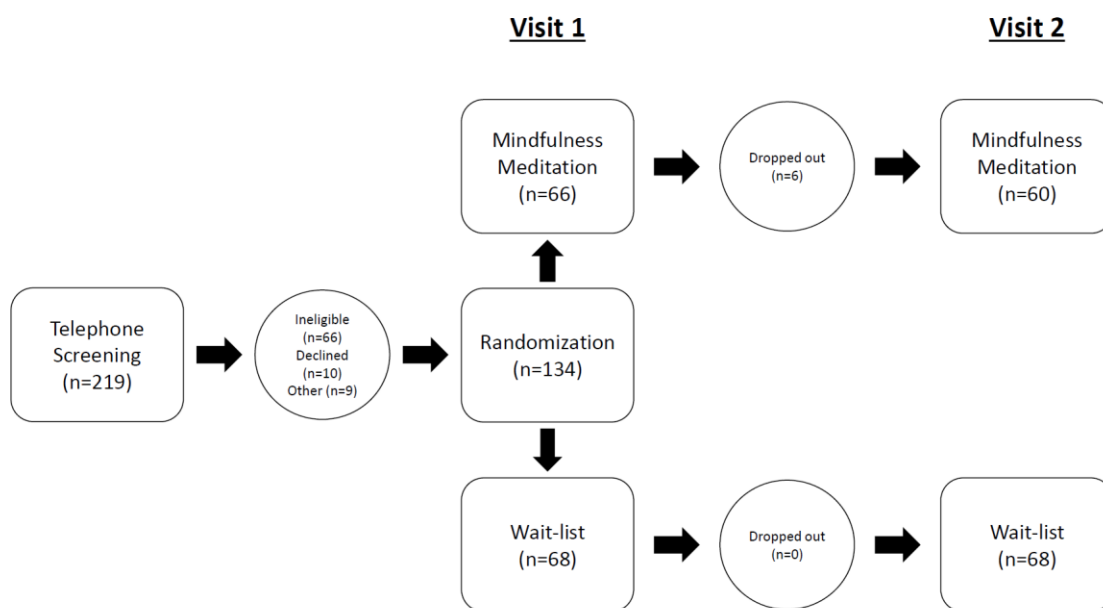


Figure 3.1. CONSORT figure.

The dropout rate by Visit 2 was only 4.5% out of 134, but the dropout rate was higher in the MM group (Fisher's Exact Test because of 0 dropouts in the wait-list group , $p=0.013$). The 6 dropouts had characteristics roughly comparable to the completers (age = 58.2 years, 4 women, education 14.5 years, and PSS 22).

Table 3.3. Outcome measures by group and effect size

Outcome Measures	Visit 1 Mean (SD)	Visit 2 Mean (SD)	Visit 1 Mean (SD)	Visit 2 Mean (SD)	Unadj <i>p</i>	FDR <i>p</i>	partial eta squared	adjusted mean differ.
Self-Rated								
NEO- N	24.8 (7.2)	20.7 (7.7)	24.4 (9.3)	23.6 (9.7)	.0001	.001**	.12	3.3
PSS	18.7 (5.9)	15.2 (5.7)	18.5 (6.1)	18.5 (7.2)	.0001	.001**	.11	3.5
CESD ¹	17.6(8.5)	12.4(7.6)	19.4(10.5)	18.5(10.9)	.0002	.002**	.11	4.9
NEO-A ¹	33.9(4.9)	36.1(5.1)	33.5(6.3)	33.6(6.2)	.0006	.003**	.09	-2.2
NEO-C	28.6(7.5)	31.0(6.3)	31.1(7.1)	30.7(7.3)	.0003	.002**	.10	-2.3
NEO-E	24.5(4.5)	25.3(4.3)	25.3(6.4)	24.8(6.7)	.03	.09	.04	-1.3
NEO-O	27.4(5.5)	28.0(5.3)	26.6(5.8)	26.5(5.1)	.10	.18	.02	-0.9
PANAS-neg (trait) ¹	21.7(6.4)	17.9(5.5)	21.9(7.5)	20.8(7.7)	.001	.005**	.08	2.7
PANAS-pos ¹ (trait)	32.1(6.3)	33.1(6.0)	32.7(7.1)	32.1(6.0)	.07	.14	.03	-1.4
PANAS-neg (state) ¹	6.5(1.7)	6.3(1.7)	6.2(1.6)	6.3(1.5)	.46	.54	.01	0.2
PANAS-pos (state) ¹	14.3(3.4)	14.6(3.4)	14.5(3.3)	14.0(3.5)	.21	.33	.02	-0.7
GPSE ¹	29.6(3.5)	30.3(3.7)	30.1(4.2)	29.2(4.0)	.003	.009*	.07	-1.5
Sf-36 fatigue ¹	39.8(19.7)	51.3(21.7)	46.5(19.4)	48.2(20.3)	.002	.008*	.08	8.3
SF-36 PCS ¹	50.4(6.5)	49.1(6.8)	50.2(6.7)	50.6(7.2)	.07	.14	.03	1.6
SF-36 MCS ¹	37.9(9.6)	44.3(9.8)	40.0(10.6)	40.3(11.5)	.00003	.001**	.13	-5.7
PSQI	8.5(3.3)	6.9(3.0)	8.4(3.2)	7.6(3.0)	.08	.16	.02	0.8
MAAS ¹	51.8(10.2)	57.6(10.1)	51.5(12.1)	54.8(11.2)	.05	.14	.03	-2.6
FFMQ-NJ ¹	30.1(6.5)	32.9(6.0)	29.5(7.0)	30.5(7.9)	.06	.14	.03	-2.0
Cognitive								
Letter Number Sequencing ¹	10.9(2.3)	11.5(2.7)	11.3(2.7)	11.6(2.7)	.61	.69	.00	-0.2
Letter fluency ¹ dyrs)	48.0(14.3)	46.9(13.4)	47.0(14.2)	49.5(14.2)	.13	.23	.03	3.2
Category fluency	21.4(5.9)	16.5(4.7)	21.4(5.6)	17.0(4.1)	.88	.94	.00	0.6
Stroop CW condition ¹	44.3(8.4)	46.4(7.6)	47.1(9.3)	49.1(7.5)	.37	.48	.01	1.1
Stroop CW interference	49.0(8.3)	48.8(7.0)	46.6(9.8)	49.5(6.8)	.38	.48	.01	1.3

Word list- delayed	6.8(2.0)	7.5(1.8)	6.8(2.0)	7.3(1.9)	.40	.49	.01	-0.2
Choice RT (msec) ¹	470(67)	462(70)	463(70)	465(59)	.21	.33	.01	7.3
Simple RT (msec) ¹	270(46)	267(43)	272(43)	279(40)	.07	.14	.03	10.0
Flanker RT Incongruent (msec)	753(107)	703(119)	792(165)	726(148)	.37	.4	.01	-3.6
Physiological								
Respiration rate 1 st five mins	14.3(2.9)	13.5(3.0)	14.1(2.9)	14.2(2.7)	.10	.18	.03	0.7
Respiration rate 2 nd five mins	14.6(2.9)	13.7(3.1)	14.2(2.8)	14.5(2.6)	.05	.09	.04	0.9
Respiration rate 3 rd five mins	14.8(2.8)	13.9(3.3)	13.9(2.9)	14.8(2.8)	.005	.01*	.09	1.5
CAR ¹	.17(.21)	.13(.20)	.05(.46)	.12(.24)	.98	.99	.00	-.01
Cortisol slope ¹	-.18(.27)	-.23(.14)	-.26(.20)	-.18(.83)	.07	.14	.03	0.1
Systolic bp	133(20)	128(20)	130(19)	128(16)	.33	.44	.01	1.5
Diastolic bp	81(13)	80(11)	80(12)	80(10)	.33	.44	.01	0.5
Heart rate	70(12)	69(12)	68(10)	68(10)	.73	.80	.00	0.4
HRV SDRR (msec)	42(21)	46(19)	41(24)	46(20)	.99	.99	.00	0.0
HRV LF/HF ratio ¹	1.9(1.5)	3.2(3.1)	2.5(2.1)	3.0(1.9)	.29	.43	.01	-0.5

Untransformed mean (standard deviation) of outcomes at the two visits by group. For ANCOVA group effect, there are unadjusted (unadj.) *p* values, FDR adjusted *p* values across all outcomes, partial eta squared effect size, and adjusted mean difference at Visit 2 (waitlist – MM). The number of participants for most analyses is 128. For FDR *p* values, * *p*<.05 and ** *p*<.005.

MM = mindfulness meditation intervention group; Unadj = unadjusted; FDR = False Discovery Rate; NEO = Neuroticism-Extraversion-Openness Personality Inventory (-N = Neuroticism; -A = Agreeableness; C=Conscientiousness; -E = Extraversion; -O = Openness); PSS = Perceived Stress Scale; CESD = Center for

Epidemiologic Studies Depression Scale; PANAS = Positive and Negative Affect Schedule (-neg = Negative Affect; -pos = Positive Affect); GPSE = General Perceived Self-Efficacy; SF-36 = Short Form 36-item health-related quality of life; PCS = Physical Component Summary Score; MCS = Mental Component Summary Score; PSQI = Pittsburgh Sleep Quality Inventory; MAAS = Mindful Attention Awareness Scale; FFMQ-NJ = Five Factor Mindfulness Questionnaire—Non-Judgmental Factor; CW = Color Word; msec = milliseconds; RT = reaction time; mins = minutes; CAR = Cortisol Awakening Response; bp = blood pressure; HRV = Heart Rate Variability; SDRR = Standard Deviation of Inter-Beat Interval; LF = Low Frequency; HF = High Frequency.

¹ Statistical transformation was used.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1.NEO-neuroticism	1																	
2.PSS	.60***	1																
3.CESD	.68***	.74***	1															
4.NEO-agreeableness	.29**	.19*	.26**	1														
5.NEO-Conscient.	-.34***	-.31***	-.33***	-.19*	1													
6.NEO-Extroversion	-.52***	-.26**	-.36***	-.27**	.23*	1												
7.NEO-Openness	-.11	.11	.05	-.12	-.14	.19*	1											
8.PANAS-neg trait (home)	.71***	.57***	.64***	.33***	-.23*	-.29**	.02	1										
9.PANAS-pos trait (home)	-.62***	-.43***	-.48***	-.17*	.44***	.63***	.15	-.40***	1									
10.PANAS-neg state (lab)	.24*	.15	.25*	.16	-.08	-.08	-.07	.32**	-.08	1								
11.PANAS-pos state (lab)	-.11	-.12	-.05	-.00	.20*	.22*	-.07	-.06	.38***	.16	1							
12.GPSE	-.42***	-.31***	-.38***	-.18*	.35***	.34***	.03	-.36***	.51***	-.21*	.12	1						
13.SF-36 Fatigue	-.49***	-.51***	-.53***	.05	.26**	.20*	-.03	-.47***	.47***	-.21*	.17	.12	1					
14.SF-36 MHC	-.62***	-.61***	-.64***	-.17*	.31***	.28***	-.09	-.59***	.50***	-.15	.24*	.11	.69***	1				
15.SF-36 PHC	.08	-.03	-.05	.04	.04	-.05	.07	-.04	-.04	-.15	-.21*	.28**	.12	-.30***	1			
16.PSQI	.17*	.06	.18*	.07	-.09	-.09	-.13	.18*	-.08	.07	.08	-.02	-.29**	-.12	-.19*	1		
17.Mindfulness – current moment	-.38***	-.34***	-.33***	-.11	.30***	.16	-.08	-.33***	.27**	.08	.15	.16	.23*	-.08	.36***	-.08	1	
18.Mindfulness - non-judgemental	-.61***	-.29***	-.41***	-.26**	.14	.29**	.08	-.52***	.23*	-.04	.08	.28**	.18*	-.04	.36***	-.14	.36***	1

Table 3.4. Correlation matrix of all normalized self-rated outcome measures, with unadjusted p values * p<.05, ** p < .005, *** p < .0005

Outcomes Analysis (Table 3.3)

The outcomes related to negative affect and stress were almost all highly significantly improved from the MM intervention after adjusting for multiple comparisons. This includes CESD, PANAS-negative (trait), and PSS with small to moderate effect sizes (e.g., partial eta squared for CESD was 0.11). The PANAS-positive was not significantly affected by the MM intervention. Although the conventional PANAS-negative completed at home using conventional questions was significantly affected by MM, the state PANAS filled out in the lab setting demonstrated no significant change from the intervention for either negative or positive affect. The test-retest reliability, as assessed by the correlation of the measure at baseline Visit 1 with the measure at Visit 2, was lower than for the PANAS state version than the trait version.

NEO personality traits were significantly affected by the intervention. NEO Neuroticism was the *a priori* personality trait affected ($p = 0.001$) but other traits also changed significantly, Agreeableness ($p=0.003$) and Conscientiousness ($p=0.002$). There was no significant change of Extraversion or Openness.

The SF-36 Energy and Fatigue demonstrated significant improvement ($p = .008$). The calculated Mental Health Composite also demonstrated significant improvement ($p<.0.001$) but the Physical Health Composite did not. Self-efficacy (GPSE) also improved with the intervention. Of note, the two mindfulness

measures were not significantly improved although there was a trend towards improvement of the mindfulness-nonjudgmental factor. Subjective sleep quality (PSQI) was not significantly improved. See Figure 3.4 for pairwise correlations between all the self-rated measures. The correlations were very high for most of the measures that were affected by the intervention suggesting some common underlying factor may be assessed by all these measures.

There were no significant intervention effects on the cognitive battery, including working memory (Letter Number Sequencing), Stroop test, verbal fluency (semantic or category), immediate or delayed verbal memory (using CERAD word list), flanker attention task, simple reaction time or choice reaction time.

Additionally, there were no significant effects on salivary cortisol (awakening response or diurnal downward slope), heart rate, or heart rate variability. There was a significant decrease in respiration rate in the MM compared to waitlist group after 10 minutes of sitting and listening to an audio recording without performing any task.

Adherence and home practice

Participants in the MM intervention attended all one-on-one training sessions (these often required rescheduling) and practiced at home an average of 30.3 +/- 11.8 minutes per day. Using linear regression in the 60 participants who received MM training before Visit 2, there was no relationship between minutes

practiced and outcome measures that were significantly affected by the MM intervention compared to wait-list.

DISCUSSION

This randomized controlled trial of six-week MM training compared to waitlist control of 134 50-85 year olds was executed adequately, maintained blinding of the assessors, and had a dropout rate of only 4% through Visit 2. The six dropouts were disproportionately all in the MM group which may be related to the fact that those in the waitlist group only needed attend the Visit 2 assessment to receive the MM intervention and they did not need attend the six weekly training sessions.

There were very significant improvements in most of the standardized, self-rated measures related to negative mood and stress. Of note, there was no significant effect for positive affect (PANAS-pos). Additionally, the assessment of stress using the PANAS state 10-question version was not sensitive to intervention. While the state version may be useful for ecological momentary assessment over many assessments and days, it does have more intra-subject variability. This may be related to the wording of the state assessment that asked “Right now I feel ___ ?” in contrast to the more commonly used standard version that asked “how you generally feel” or “how you feel on average”.

Neuroticism was specifically analyzed as an outcome even though it correlates with other negative affect measures. While personality has been thought of more

as a stable trait measure with genetic contributions, personality as assessed with measures such as the NEO is affected by environmental influences and has been reported to change both negatively with chronic caregiver stress [30] or positively from a meditation intervention [264]. While Neuroticism was the most altered of the personality traits (decreased), Conscientiousness and Agreeableness also changed (increased) in response to the MM intervention; Extraversion and Openness did not change.

The SF-36 health related quality of life demonstrated significant changes in the Mental Health Composite and Vitality subscore. The average improvement in the Mental Health Composite (6.4) was greater than the minimum clinically important difference which is 4 [265] with the wait-list increasing by 0.3 and the average improvement in the Vitality subscore was 11.5, more than the minimum clinically important difference of about 9 [265] with the wait-list group increasing by 1.7. The vitality component of the SF-36 was previously improved from a mind-body intervention (yoga) in healthy older adults [242] and in people with multiple sclerosis [241].

Self-efficacy (GPSE) improved from the intervention although less than some of the negative affect measures. Subjective sleep quality (PSQI) did not improve even though there has been suggestion of improved sleep in mind-body interventions [248]. Our study participants were not recruited for sleep problems although participants did have some sleep problems overall, with an average PSQI at baseline of 8.4

With the exception of respiration rate, the cognitive and physiological outcomes were not changed. The decline in respiration rate in the MM group was seen in the third 5-minute block of sitting quietly listening to auditory recordings and it may represent a specific training related change since awareness of breathing was part of the training. This finding that meditation produced benefits in psychological measures but not in objective physiological measures is consistent with some meta-analyses of meditation interventions [225, 266]. However, this trend in the literature contrasts with many individual MM intervention studies demonstrating some effect on physiological and cognitive outcomes with intervention lengths both longer and shorter than 6 weeks [98-105]. Due to the wait-list only control it could be that some benefit of the MM compared to wait-list may be related to simple attention and expectancy/placebo effects. The fact that objective measures demonstrated less change than the subjective self-rated measures, lends credibility to this possibility since placebo is known to have a greater effect on subjective measures [115, 267]. However, some of the highly standardized assessments such as Neuroticism are not generally known to have significant improvements from any intervention, let alone demonstrate a placebo effect. Also, the significant changes in the psychological measures were not correlated with expectancy.

The lack of changes in cognitive outcomes despite the known relationships of cognition to chronic stress especially with aging [26, 28, 117] is of interest since it is known that excessive stress has a negative effect on cognitive function; thus,

we must question why no changes were seen with improved self-rated stress. The participants did not have pathological depression, PTSD, or anxiety disorders that are more likely to produce impairments in cognition and so our participants may have been performing at or near their maximal ability already. Over the 2-month study, perhaps the selected cognitive measures were not optimal even though it was a fairly broad battery with a focus on frontal/executive measures that are known to be more sensitive to negative affect and stress. The cognitive benefits of MM may be related to decreased mind-wandering [268 Hasenkamp, 2012 #5525, 269, 270] which may not be apparent in conventional cognitive testing where high attentional focus is required only for relatively brief periods.

There were essentially no changes in the physiological measures related to stress. There were no changes in HRV (LF/HF ratio and standard deviation of RR interval) or cortisol, which were strong theoretical candidates for sensitive measures. We sampled cortisol only three times a day over two days at each of the visits. This limitation in design was associated with poor intra-subject reliability for test-retest, high inter-subject coefficient of variation, and limited ability to calculate area under the curve or diurnal cortisol slope. Thus, the study design may have been at least partially responsible for the lack of significant change.

The lack of major changes in objective measures in contrast to the self-rated measures is likely not related only to placebo effect issues and potential explanations are provided.

- 1) It is possible that the MM intervention was not a sufficiently long duration.
- 2) The one-on-one class is likely not ideal for all participants although it has been quite acceptable and allows more flexibility in scheduling research participants. A recent survey comparing on-line, one-on-one and group delivery of meditation training suggested that one-on-one was at least as favorable as group [231]. A group setting might have produced some improvements because of group dynamics but group dynamics would add experimental noise to the intervention, and a group setting is less acceptable to some people, e.g., those with high introversion or PTSD.
- 3) There are many physiological measures related to stress [224] which may increase due to a short term stressor but perhaps not decrease that much secondary to a longer term stress-reducing intervention. Other physiological changes not directly related to intracerebral processes such as telomerase or what have been called allostatic load measures have generally been more sensitive to longer term cross-sectional differences [141, 180-183, 212, 271] and may have similarly low sensitivity to a broad population intervention.
- 4) The outcomes may need to be measured over a much longer time frame or follow-up since physiological changes related to stress improvement

may take considerable time (Visit 2 was at two months). For example hair cortisol and hippocampal size reflect stress-induced changes over a longer term even though they are not necessarily sensitive to acute or excessive transient responses [14, 166, 272].

- 5) The outcomes may not be optimally chosen or well-performed. While we have previously demonstrated experimental and cross-sectional changes in cortisol and heart rate variability [153, 273], cortisol is known to have high test retest variability and sampling at only three time points on only two days may be contributing to the absence of an intervention effect.
- 6.) Ecological Momentary Assessment (EMA) is different from the more commonly performed single assessments especially if done in in the laboratory environment. The laboratory induces an inherent change in peoples' state, and they are not exposed to the usual environmental stressors that would demonstrate their negative emotional reactivity and coping mechanisms. This is particularly problematic for studies involving the effects of stress where EMA has been used [194, 195, 274, 275]. While the PANAS state version that would be closer to what is asked using EMA had more intrasubject variability, recording it many times over many days may actually capture reactivity to real-life stressors. Additionally, EMA may be preferable because assessments in the research lab setting may be unrealistic. For example, in a prior study of stressed older adults (dementia caregivers), participants were often

relieved to be away from their caregiving responsibilities for the time they were in the laboratory and thus had lower stress in the lab compared to home - in contrast to control subjects who had mildly increased stress in lab compared to home [276].

- 7.) The improvements related to meditation may primarily improve responsiveness to stressor (resilience). The objective measures may need to be direct measures of resilience to stress either with experimental stressors or more sustained ecological momentary assessment. For example, cortisol on an average assessment day may be less affected than cortisol in response to a stressor.
- 8.) It is likely that some people do not improve as a result of MM training from a physiological, cognitive, or even mental health perspective. It will be useful to better define those most likely to respond to MM training.
- 9.) It is likely that different people have different physiological effects of stress. For example, some people may develop stress effects on their blood pressure, some on their gastrointestinal system, and some on their cognitive function.
- 10.) There is no way to assess the quality of meditation so it is possible that the “dose” as measured in number of hours practiced was insufficient in this study to induce cognitive or physiological changes.

As mentioned above , the optimal dose of meditation needed to induce stress-

relieving cognitive or physiological effects is not known. Those in this MM study practiced an average of 28 minutes per day during the 6-week intervention as assessed by turning on the study iPod to listen to the guided meditation audio for daily practice. Among the self-rated psychological measures that did demonstrate improvement with MM training compared to wait-list, there was no relationship of the degree of improvement with minutes practiced. There is little empirical data to justify how long one should practice meditation to achieve improvements in clinically relevant markers, and it would be helpful to have better knowledge of the dose response effect.

There are several additional limitations of this study. The age range of the study population was relatively narrow and participants were mostly Caucasian and highly educated. While participants needed to report at least mild stress, they were not allowed to have very significant stress attributable to conditions such as generalized anxiety disorder, PTSD or untreated depression. The latter populations may demonstrate different effects of MM on cognitive or physiological outcomes.

This study demonstrated very significant improvement in many self-rated measures related to negative affect and stress, including clinically significant improvements in health-related quality of life and a decrease in neuroticism. While possible explanations for the lack of changes in cognitive and physiological

measures have already been discussed, there remains a need for more complex experimental and analytical approaches to understand the improvement in mental health from MM. Since reactivity to stress is a biologically complicated system and different people have different physiological sequelae to stress, researchers may well benefit from methodologies that generate more relevant data and take better advantage of systems science methods and approaches [119, 224].

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Conflicts of Interest and Source of Funding.

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Preliminary results were presented at the International Research Conference on Integrative Medicine and Health 2014 annual meeting [42].

Chapter 4.

Predictors of improvements in mental health to mindfulness meditation intervention in healthy, stressed older adults using decision tree machine learning.

Objective: To determine if machine learning can generate a reliable classifier to predict who will benefit from a mindfulness meditation (MM) intervention.

Methods: 134 stressed 50-85 year olds were randomized to an MM intervention with six weekly one-on-one sessions with a trainer along with home practice or to a wait-list control (ClinicalTrials.gov NCT01386060). Outcome measures were assessed at baseline, Visit 2, and Visit 3 (two months apart). All participants received the MM intervention either between baseline and Visit 2 or between Visit 2 and Visit 3 (wait-list). A responder was defined by comparing their baseline and immediate post-MM intervention data using a known minimum clinically important difference of the SF-36 health related quality of life mental health component. There were 121 participants who completed their MM training with baseline assessments and post-MM outcomes. Seventeen potential predictors included demographic information (gender, age, and years of education) and selected self-rated baseline measures related to stress and affect. Continuous predictors were normalized if necessary and all were standardized using the Z transformation. Simple univariate statistical analysis was performed to compare the values for the predictors in the responder and non-responder groups. Next, nine predictors were chosen for the machine

learning analysis based on other results and *a priori* rationales. In addition to choosing nine predictors for the machine learning analysis, principal component analysis (PCA) was performed on all 17 baseline measures to reduce the number of input variables to the classifier. Classification was performed using decision tree analysis with 10-fold cross-validation. The reliability of the classifier was calculated as the mean and standard error across the classifiers.

Results. 121 participants completed their MM intervention having data from before and after their meditation training. As defined using the SF-36 mental health component, there were 61 responders and 60 non-responders. Univariate statistical analysis of the baseline measures demonstrated significant differences between the responder and non-responders in several measures including the Positive and Negative Affect Schedule negative (PANAS-neg), SF-36 Mental Health Component (SF36-MHC), SF-36 Energy, the maximum PANAS-neg (state version) of four ecological momentary assessments using smartphones at home, and Neuroticism-Extraversion-Openness (NEO) personality assessment of neuroticism. Decision tree analyses using 4 or 9 a priori or PCA chosen predictors were unable to achieve reliable classification rate of better than 65%.

Discussion: Several differences in predictor variable were observed between responders and non-responders to a MM intervention but decision tree analysis was unable to usefully predict who would respond to the intervention. Several

limitations to the analysis and future directions are discussed.

Keywords (up to six)

Meditation, responder, decision tree machine learning, stress, mental health, older adults

Abbreviations/acronyms

CESD – Center for Epidemiologic Studies Depression

EMA- ecological momentary assessment

GPSE – General Perceived Self-Efficacy

MM – mindfulness meditation

MHC – Mental Health Component (of the SF-36)

NEO – Neuroticism-Extraversion-Openness

PANAS – Positive and negative affect schedule

PANAS-neg-max – maximum PANAS-negative of the 4 at-home EMA assessments

PCA – principal component analysis

PSQI - Pittsburgh Sleep Quality Inventory

PSS – Perceived Stress Scale

SF-36 – Short form 36-item health related quality of life

Mindfulness meditation (MM) is a popular meditation approach that has already been formally studied and applied in a variety of clinical conditions including Post-Traumatic Stress Disorder, depression, pain, and stress.[75-83] However, the evidence for efficacy has not been as compelling as it could be [84, 85] and one possible explanation may be that not everyone will improve with MM training. This analysis hopes to shed light on who may be most likely to benefit from MM training.

The most evidence of benefits of MM intervention is from improvements in self-rated stress and mental health [86, 225]. Given the complexity of the stress system including multiple causative factors, mediators and physiological outputs [224, 277, 278], it is likely that some people benefit significantly while others may not benefit at all. It would be helpful to know from a clinical perspective as well as from a research perspective of better understanding the mechanism of MM benefit, what factors might predict clinically significant improvements of MM. Despite reported improvements following meditation interventions, there has been limited research into what factors predict or moderate the benefits of MM. At least some measures of baseline affect impact on response to meditation treatment.

This analysis was performed to determine if and which baseline assessments will predict who may most likely be a responder, i.e., benefit from MM training. The prediction analysis utilized a machine learning approach, more specifically decision-tree analysis [279].

METHODS.

Participants

Participants consisted of generally healthy adults 50-85 years of age who reported at least mild levels of stress. Participants were recruited from the greater Portland, Oregon metropolitan area. Following inquiries, participants were told about the study and eligibility criteria. If interested, they underwent a 30-minute telephone inclusion screening for which there was an IRB-approved Waiver of Authorization. This study was approved by the Oregon Health & Sciences University Institutional Review Board (IRB) and was registered with ClinicalTrials.gov (NCT01386060). Participants provided informed consent at Visit 1 at the research lab. Exclusion criteria were primarily to screen out an underlying illness that might limit the benefit of the intervention, confound outcomes, or increase the likelihood of dropout (Table 4.1).

Table 4.1. Inclusion and exclusion criteria

Inclusion Criteria	<ul style="list-style-type: none"> • Age 50-85 years old; • Baseline Perceived Stress Scale (PSS) [228] score ≥ 9; • Agree to follow the study protocol including randomization;
Exclusion Criteria	<ul style="list-style-type: none"> • Cognitive impairment (significant participant complaints) or a score of less < 30 on the Modified Telephone Interview for Cognitive Status (TICS-m) [229] • Significant patient-reported medical/neurologic disease (e.g., major organ failure; insulin-dependent diabetes, active cancer, or alcoholism); • Significant, untreated depression. Significant was defined based on Geriatric Depression Scale greater than 5 and interview; • Take medications known to affect CNS function or impact physiologic measures (e.g., steroids, neuroleptics or regular narcotic analgesics); stable doses of CNS-active drugs with less impact (e.g., beta-blockers, SSRI's, and histamine blockers) were acceptable; enrolled participants were encouraged not to change their drug use during the study period and to inform the investigator if any change was made. • Cannot understand the instructions (e.g., cannot hear or see study materials or not fluent in English); • Prior experience with meditation classes or other mind-body classes (e.g., yoga or tai chi) within the last 24 months or more than 5 minutes daily practice in the last 30 days.

Following Visit 1, all randomizations were performed by non-blinded research personnel using a computerized covariate adaptive randomization procedure [230] aimed at balancing active and waitlist groups on age, gender, and baseline Perceived Stress Scale score using a pre-determined projected median split for

the continuous measures. The researcher who led the meditation training sessions performed the randomization, and the research assistants who conducted data-collection visits remained blinded. There were three testing visits (Figure 4.1), each 2 months apart, and all participants received a 6-week MM training either between Visits 1 and 2 or between Visits 2 and 3 (wait-list control). Participants who received the intervention post-Visit 2 served as a wait-list control for the primary outcome analyses at Visit 2 previously described in chapter 3. For the definition of responder for this analysis, pre-MM intervention data were subtracted from the immediate post-MM data.

Intervention

The MM intervention was administered in six, one-on-one sessions occurring weekly either between Visit 1 and Visit 2, or between Visit 2 and Visit 3 (wait-list control). More details of the intervention that was a standardized and structured program based on Mindfulness Based Cognitive Therapy [232, 233] are described in Chapter 3 and a prior publication [280]. An unblinded RA delivered the one-on-one training sessions but the assessments were performed by blinded RAs. In addition to the six 60-90 minute training sessions, daily guided meditations for home practice were accessed with a study iPod and adherence tracked with developed software, iMINDr [281]. Participants were instructed to practice at home up to 30 minutes a day as a goal but at least do some daily practice. MM sessions offered strategies other than meditation for practicing

mindfulness skills to cope with the many stressors that adults typically face.

Participants who were randomized to the Wait-list arm between Visit 1 and Visit 2 received the MM intervention after the wait-list period (between Visit 2 and Visit 3). All participants randomized to wait-list group had the same MM training in the Visit 2-Visit 3 period as those randomized to receive MM immediately after Visit 1.

ANALYSIS

This is an exploratory analysis to determine if one can predict who will improve from MM training and, if so, which predictor variables contribute to this classifier. The outcome variable that demonstrated the greatest effect size in the previous analyses (Chapter 3) and is also moderately clinically significant was used to define “responder” based on their improvement immediately following MM training.

Outcomes used to define responder

For more detail of the outcomes, some of which are also used as predictors when measured at baseline, please refer to Chapter 3. Further details of the specific measure used to define who was a responder and predictors of being a responder are given below. For this analysis, a responder is someone who achieved a minimum clinically important difference improvement in SF-36 Mental Health Component which is 4 [265].

Predictors

Since there were only 121 participants in this analysis, a decision was made to limit the machine learning analysis to only 9 predictors. One set of analyses utilized nine predictors chosen based on *a priori* hypotheses. Another set of analyses was performed using only nine final predictors but chosen instead based on principal component analysis (PCA) so all demographic and self-rated psychological measures could be potentially included in the analysis. A second set of analyses were performed with just 4 predictors in case there were limitations in machine learning related to overfitting or to multicollinearity of the input predictors. All participants who completed the MM intervention were used for these analyses.

Demographic measures were gender, age, years of education, annual income and lifetime exposure to stressful events measure [282].

Self-rated measures obtained at baseline Visit 1 and potentially entered into the predictor analysis are self-rated measures that might affect responsiveness to the MM intervention.

- **Stress.** The Perceived Stress Scale [228] and the PANAS [236] were administered. At home on a Smartphone assessment tool, participants answered the state question PANAS [236, 238] a reduced 10-question version [239] four

semi-random times over waking hours, and the maximum PANAS-negative across the home assessments at baseline was used as a predictor.

- Neuroticism. While neuroticism has been considered a stable trait, changes in neuroticism are a possible outcome from meditation studies [42, 212].

Neuroticism assessed with the current NEO [202] is used both as a predictor as well as helping to define one of the secondary responder definitions.

- Mood. Depression was assessed by the Center for Epidemiologic Studies Depression Scale (CESD) [237].
- Fatigue. The 4-question Energy and Fatigue subscale of the SF-36 health-related quality of life [240] that was previously found to be sensitive to yoga in two prior studies [241, 242] may be a predictor of responsiveness.
- Self-efficacy. A measure of self-efficacy, the General Perceived Self-Efficacy Scale [244], was included because of participants' reporting their sense of control was significantly affected by meditation [107, 245, 246].
- Mindfulness. A measure of mindfulness from the Five Factor Mindfulness Questionnaire [88] was used as a predictor. Factor 5, mindful non-judging, was used because it was found in prior studies to be significantly different in chronically stressed populations, i.e., it was different between veterans with and without post-traumatic stress-disorder [211] and between dementia caregivers and non-caregivers [30].
- Stressful life events experienced measure was assessed with the Life Experiences Survey [282].

- Expectancy/Credibility was assessed [250] by using the sum of the components.

Analysis: Conventional descriptive statistics

For descriptive purposes, the means of the 15 baseline continuous predictors were compared between the responders and non-responder groups using t-tests with unadjusted p values calculated as well as false discovery rates. Income that was assessed using a 7-step scale was compared using Wilcoxon rank order and the distribution of gender was assessed using chi-square.

Analysis: Machine learning approach.

Data processing was first performed in Stata 14 (StataCorp, College Station TX). All predictors and the outcomes to be predicted were checked for normality using Shapiro-Wilk and transformed if distributions were not normal (e.g., square root or Box-Cox to correct for skewness) even though this likely would not impact the decision tree analysis. The rest of the analyses were performed in Matlab (MathWorks, Natick, MA) including the Statistics and Machine Learning Toolbox. All baseline predictor measures were next standardized by dividing by the baseline predictor standard deviation across all the participants.

The classifier used decision tree analysis for classification of responder or non-responder as defined above. Decision tree analysis was chosen in part because of the small sample size, its ability to deal with missing data, and because the

decision tree is more interpretable to other researchers in the field as compared to other approaches such as support vector machine. Of note, PCA without rotation or other adjustment may negate the interpretability benefit. The Matlab function *fitctree* uses a greedy decision algorithm based on iterative dichomization (ID3) [283] and with other enhancements or additions including how decisions regarding split nodes are made (e.g., information gain or Gini index) and pruning. The greedy ID3 algorithm, that takes the feature for the next node with the highest information gain, will tend to overfit so performance often benefits from pruning (developed in the C4.5 algorithm). The algorithm copes with missing predictor values by using all available relevant data to evaluate a specific branch point although it cannot utilize participants with missing classification of responder status data.

For the first set of analyses, nine predictors were chosen that had the best *a priori* rationale based on previous literature and knowledge of the predictors and outcome: age, years of education, stressor life events, non-judgmental mindfulness, Pittsburgh Sleep Quality Index, NEO-neuroticism, SF-36 Energy and Fatigue, Expectancy, and maximum PANAS-negative using smart-phone at home assessments. Since overfitting is a concern, similar analyses were performed with only four predictors: life events, SF-36 Energy and Fatigue, NEO-neuroticism, and expectancy, For the second set of analyses, dimensionality reduction was performed by applying PCA to all the baseline measures (17) and

using the participant data from the nine components with the highest variance explained. The full data set of 17 predictor measures with only 121 participants may not generate the best classifier because of overfitting and because of errors in decision tree learning related to multicollinearity. These issues may well occur with only nine predictors as well even though there would be greater than 10 observations per predictor variable (an acceptable recommended number). Thus, a similar analysis was performed with just the four components with the most variance explained.

There were several hyperparameters for the decision tree analyses that needed to be defined including tree depth using maximum number of splits and minimum parent size as well as split criteria (maximum deviance reduction/cross-entropy vs Gini index). Of note, `fitctree` forces the minimum parent size (`MinParentSize`) to be linked to minimum number of leaf node observations size (`MinLeafSize`), i.e., $\text{MinParentSize} = \max(\text{MinParentSize}, 2 * \text{MinLeafSize})$. Thus parent size cannot be modified independently of leaf size and the two potential parameters represent only one actual hyperparameter. Since there was concern about trying to define too many hyperparameters even before generating the decision tree classifier given the small data set, two parameters were defined a priori: the split criterion was the maximum deviance reduction and pruning was set to “on” which only sets the optimal sequence of pruned subtrees. Given the limited data set

size, the Matlab default tree definition parameters were chosen for the other hyperparameters.

Once the hyperparameters were decided on, the model was generated using the full data set ($n=121$). The reliability of the classifier was evaluated by using a 10-fold cross-validation and generating the mean of the classification error along with the standard error using the Matlab function *cvloss*. Since one goal was to help predict who will most likely benefit from MM training, the average information gain from the predictors in any useful classifier would be determined along with their mean and standard error.

RESULTS

See Figure 4.1 for the clinical trial study design with recruitment, randomization, and drop-out numbers. See table 4.2 for demographics and selected baseline measures for all participants who completed their MM training and were used for these analyses. Of the 121 completers, the average age was 60 years and 79% were women. Half were considered responders based on the SF-36 mental health component. The completers practiced meditation 27.0 ± 10.7 mins per day during their intervention period.

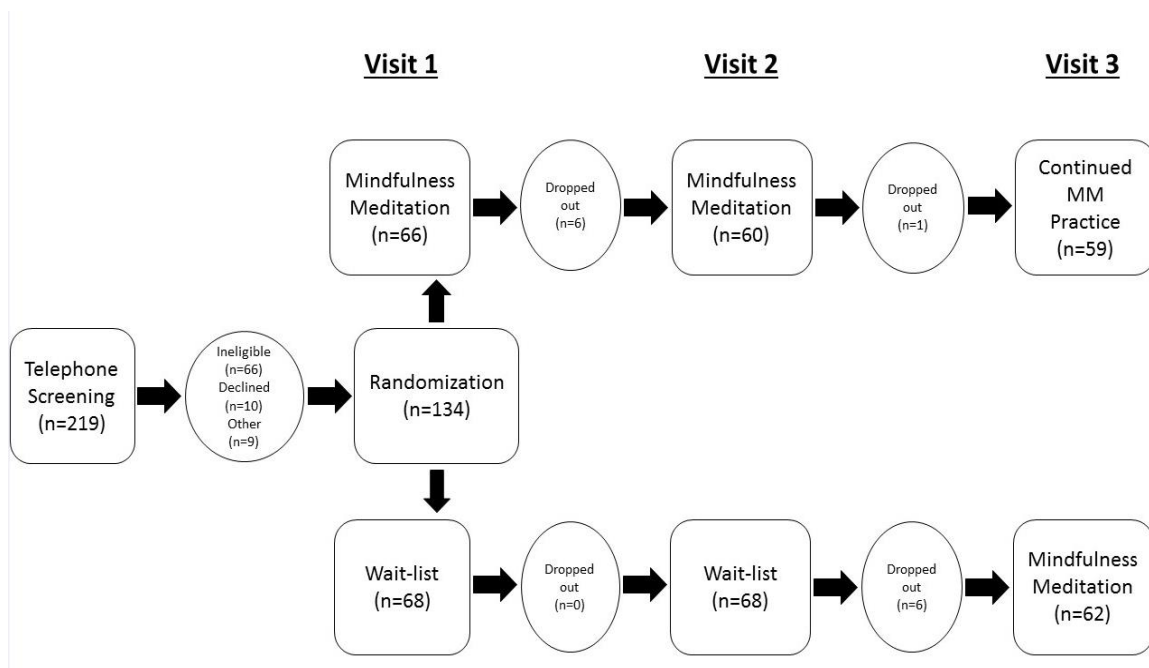


Figure 4.1. Consort table.

Table 4.2. Demographics and predictor variables. Mean (standard deviation) grouped by responder status as defined by the minimum clinically important difference of the SF-36 MHC from the 121 participants who completed the MM intervention. Statistics comparing the 2 groups are given (by t for all except chi-square for gender and Wilcoxon rank order for 7-step income) and associated p values and false discovery rate adjusted p values.

	SF36-MHC responder n=61	SF-36 MHC non-responder n=60	Statistic, p value, and FDR adjusted p value		
Female (%)	51 (84%)	45 (75%)	1.37	p=0.24	0.47
Age (years)	59.0 (6.7)	60.8 (7.1)	-1.37	p=.17	0.41
Years of Education	16.9 (2.9)	16.6 (2.4)	0.60	p = .55	-.62
Income (7 steps)	4.6 (2.1)	4.3 (2.0)	0.78	p = 0.43	0.53
Life Event stressors	-10.4	-6.9	-1.58	p=0.12	0.34
PSS (baseline)	19.0 (6.1)	17.8 (5.5)	1.07	p = 0.29	0.47
PANAS-neg	23.2 (7.9)	19.8 (5.4)	2.77	p = 0.0065*	0.04*
PANAS-pos	32.4 (6.9)	33.3 (6.0)	-0.77	p = 0.44	0.53
PANAS-neg-max home	8.6 (3.2)	7.3 (2.3)	2.40	p = 0.018*	0.08
NEO-neuroticism	25.8 (8.2)	22.8 (8.2)	1.98	p = .05*	0.17
CESD	18.9 (10.5)	17.0 (9.4)	1.16	p=0.25	0.47
SF-36 MHC	36.1 (9.5)	42.7 (9.8)	-3.77	p = 0.0003*	0.005*
SF-36 Energy	38.9 (19.1)	48.9 (19.7)	-3.1	p= .005*	0.03*
GPSE	29.7 (4.2)	30.3 (3.5)	-0.97	p = .33	0.47
PSQI	8.3 (3.0)	8.3 (3.5)	-0.01	p=0.99	0.99
Mindfulness-non-judgmental	29.4 (6.4)	30.5 (6.8)	-0.97	p = 0.33	0.47
Expectancy	28.6 (5.8)	28.3 (6.4)	0.31	p =0.75	0.80

MHC- mental health component of SF-36 health related quality of life; FDR = False Discovery Rate; PSS = Perceived Stress Scale; PANAS = Positive and Negative Affect Schedule (-neg = Negative Affect; -pos = Positive Affect); NEO = Neuroticism-Extraversion-Openness Personality Inventory; CESD = Center for Epidemiologic Studies Depression Scale; SF-36 = Short Form health related quality of life; GPSE = General Perceived Self-Efficacy; SF-36 = Short Form 36-item health-related quality of life; PSQI = Pittsburgh Sleep Quality Inventory.

The results from conventional univariate biostatistics are shown in Table 4.2. Several of the predictors were significantly different between the two groups, i.e., PANAS-neg, PANAS-neg-max at home, NEO-neuroticism, SF-36-mhc, and SF36-energy and three remained significant after correction using the false discovery rate: SF-36-mhc, SF-36-energy, and PANAS-neg.

The hyperparameter settings of tree depth and minimum parent size had little effect on the overall accuracy.

Although these settings were occasionally altered for exploratory purposes, the Matlab default settings were used for final analyses. Following the definition of the hyperparameters, the decision tree analysis utilized the nine measures that were most statistically different in the responder and non-responder groups: Life Events, age, gender, CESD, SF36-mhc SF-36-energy, NEO-neuroticism, PANAS-neg, and the PANAS_neg-max at home.. The decision tree generated from the full data set generated a mean error rate of 0.388 using 10-fold cross-validation with a standard error of 0.04. By altering input variables the decision tree was able to achieve up to a 0.347 error rate with cross-validation (standard error 0.04) but some decision trees still ended up with error rates of up to 0.444 using 10-fold cross-validation with a similar standard error. Since overfitting was always a concern, the same analysis was also done with only 4 predictors. These decision tree classifier results were similar to those already described with 10-

fold cross-validation error rates of 0.41 and standard error of 0.04 across 10-fold cross validation.

The next step in the analysis was to use PCA to reduce the number of variables and try to capture the most unexplained variance. For this measure calculation gender was not entered and the 9 components with the highest amount of variance explained were chosen. The error rates were not improved (0.46 +/- .04). Even reducing the number of variables again, by using just the 4 components with the most variance explained, did not produce any significant improvement.

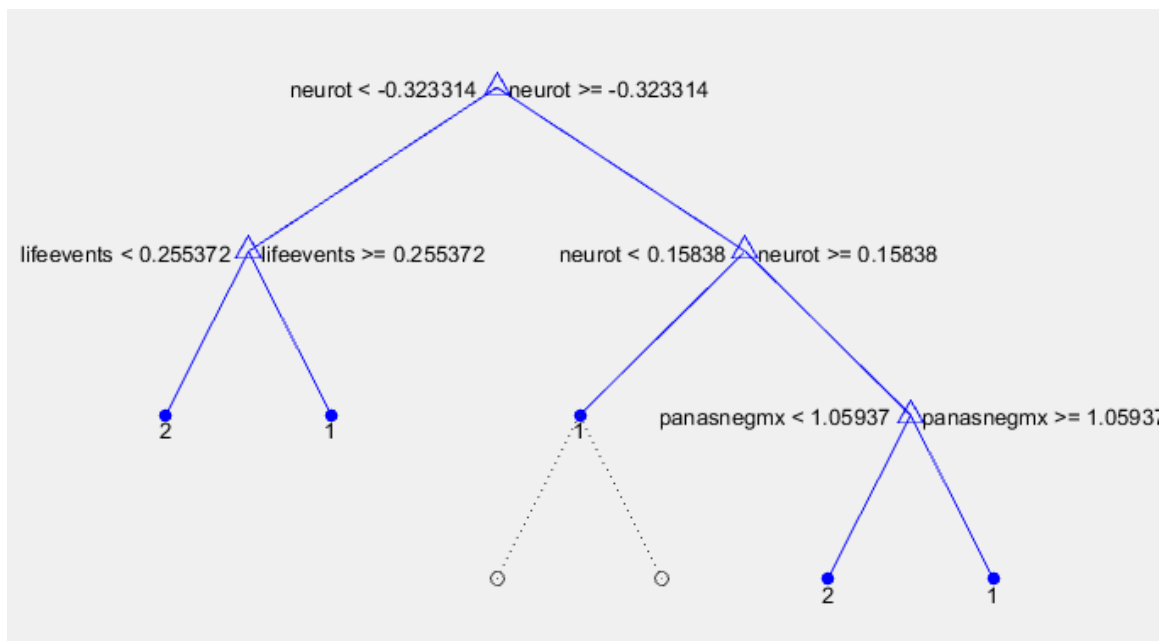


Figure 4.2. Example of decision tree classification. One decision tree in the analysis using 4 predictors yielding a 10-fold cross-validation error rate of $45\% \pm 3\%$. Fitctree settings were maximum number of splits = 5 and minimum parent size = 4. 1 is responder to MM training and 2 is a non-responder. This is level one pruning with one node eliminated. The 4 predictors entered in this analysis were Neurot = NEO-neuroticism, panasnegmx= maximum PANAS-neg from the 4 at home ecological momentary assessments, Life Events, and expectancy,

DISCUSSION

Analysis of the responders and non-responders to MM training revealed several significant differences in baseline measures. More specifically, those who improved from MM training had worse mental health prior to randomization than those who did not respond. The mental health measures that were different at baseline were the PANAS-neg, NEO-neuroticism, SF-36 Energy and Fatigue, and the SF-36 Mental Health Component, the latter also being what was used to define a responder. Machine learning using decision tree analysis to predict whether or not participant's mental health would improve following MM training had limited ability to correctly classify a participant as a responder or non-responder, with accuracy rates below 70% for almost all of the analyses and sometimes below 60%. The baseline measures that did appear in the decision tree classifiers were the ones already mentioned that were different at baseline using univariate statistics. The only other measures that occasionally appeared in the classifiers were the Life Events and expectancy measures. Mindfulness (non-judgmental), positive affect, sleep quality, and self-efficacy were also not useful at differentiating responder status. None of the demographic predictors including age, income, and gender were useful and they did not enter into the decision trees. Additionally, none of these latter measures were significantly different in responder and non-responder groups using conventional biostatistics (all p 's greater than 0.2). Besides the present study showing that those with worse mental health improve more from a meditation intervention, other studies described below have also observed that those with worse mental health at

baseline are more likely to demonstrate improvements from a meditation intervention.

One study looking specifically at the outcome of relapse in depression, observed that Mindfulness-Based Cognitive Therapy was most effective in those who had already had three or more episodes of depression and also in those whose depression was not preceded by life events [284]. One study did observe an increased effect of meditation intervention on mental distress and well-being in those with higher neuroticism [285]. Personality traits have been observed to potentially be a factor in response to other mind-body therapies as well.

Qualitative analysis (participant interview) suggested that some personality traits may predict who would respond to broader integrative medicine approach including yoga for asthma management [286]. One paper found those with greater mindfulness had greater declines in perceived stress at one year following the MM intervention [287]. The fact that those who responded to the intervention had greater fatigue at baseline is of interest. Also, of the measures that were different in the responder and non-responder groups, we had previously shown that the SF-36 Energy and Fatigue subscore was sensitive to a mind-body intervention in two randomized controlled trials of 6 months of yoga compared to control, one in a group of 69 people with multiple sclerosis [288] and one in a group of 135 healthy older adults.[242].

At least one other study also found no relationship of outcomes to baseline demographic factors, i.e., there was no relationship of demographics, baseline spirituality, or trait mindfulness on the decrease in depressive symptoms following MBSR [289]. Some researchers have simply determined changes in non-primary outcome measures, potentially at an earlier point in time than the final outcome measures, to see if those may predict outcome measure changes [113, 290], but this approach is inherently different than trying to determine predictors at baseline prior to the intervention.

Expectancy has an impact on many outcomes, self-rated outcomes in particular [115, 267]. In regards to meditation, patients with cancer had greater improvement if they were assigned to their program preference whatever program they happened to be randomized to: Mindfulness-Based Cancer Recovery, Supportive Expressive Therapy or a stress management seminar [291]. Of note, the mindfulness intervention was the most preferred program, but those randomized to their preferred intervention improved more over time on quality of life regardless of actual intervention type. Women with greater psychological morbidity at baseline showed greater improvement in stress symptoms and quality of life if they received their preferred vs non-preferred program [291]

In addition to studies discussing baseline factors that relate to improvements from the meditation interventions, there have been previous studies of MM that discussed factors associated with adherence to the MM intervention. Predicting adherence may be important since adherence to meditation practice [292] or adherence to any intervention including taking placebo may correlate with better outcomes [115]. Most studies related to adherence to a meditation intervention predictor identify factors, e.g., comorbid personality disorders, associated with completing the intervention [113]. It is known that there are a number of other factors associated with adherence to mind-body interventions which may impact outcomes [293]. This has even been extended to fMRI activation in selected brain regions predicting engagement with meditation techniques [294].

Additionally in terms of predicting adherence, the degree of stress-related physiological responses did not predict amount of meditation practice time even though the physiological measures did respond to the meditation intervention [295]. Furthermore, unrealistic positive expectations have not been found to relate to meditation practice [296]. A larger study evaluating factors predicting barriers to meditation practice found no impact of age but did find an impact of personality trait (Conscientiousness, Neuroticism, and Openness) [297].

There were several limitations to this study. Having only a wait-list control implies that some benefit of the MM compared to wait-wait-list may be related to placebo effects [115]. If this were the case, there would be two types of response

contributing to the outcome analysis: 1) placebo responsiveness predicted by certain variables such as expectancy, and 2) responsiveness to the MM intervention predicted by other variables such as mental health. The number of observations (participants) is small for a machine learning approach even though the analysis limited the number of predictors to nine so that there were more than 10 observations per variable in the training set. Decision tree analysis might have slightly benefited from methods such as ensemble learning or AdaBoost [298] methods. Additionally, decision tree analysis may not be the best machine learning approach for this data set [299]. Also, adding costs or penalties of allocation and misallocation to the decision analysis might make the analysis more interpretable but at this low level of classification accuracy it was not likely to be useful. A more general issue with predictor analysis in clinical trials is that responder status is subject to a “regression to the mean” effect, especially since many of the predictor variables are correlated to the SF-36 MHC score. Thus, those with lower SF-36 MHC will be more likely to improve, and many of the self-rated predictors are correlated with the SF-36 MHC (e.g., SF-36 energy, NEO-neuroticism, PANAS-neg). One prior study did suggest that regression to the mean is not the only explanation of beneficial MM effects. People with panic disorder receiving mindfulness-based cognitive therapy demonstrated greater improvements in their panic disorder symptoms if they were less depressed at baseline based on Hamilton Depression Rating Scale [113]. This implies that the responders had some relevant characteristic to predict responsiveness and,

given the pattern of changes, it was not simply demonstrating regression to the mean for people who have more extreme baseline values. Additionally, while not the focus of this paper, the participants in the wait-list control arm of this study had no major changes in their measures of stress and negative affect during the wait-list period (Visit 1 to Visit 2) also suggesting that regression to the mean is not the only issue. An additional limitation of the study is the lack of variability in the study sample demographics consisting of mostly highly educated women in a relatively narrow age range (50-85 years old) may limit both the quantitative analysis and the generalizability. The prevalence of women is common in mind-body intervention studies. Broader inclusion criteria for the next study would be helpful.

Future directions include the need to improve predictor analysis. Even though simple univariate analyses demonstrated that some baseline predictors were significantly different in the responder and non-responder groups (NEO-neuroticism, maximum PANAS-neg at home, SF-36 Energy and Fatigue), the decision-tree analysis was not useful for classification. Interactions of the variables may need to be better captured. Machine learning is a broad field and other techniques may be better for this type of data [299-301]. Additionally, it is likely that these particular predictor variables are not capturing salient properties of a person vis-a-vis responding to MM intervention due to the dynamic character of MM. Stress reactivity rather than simply perceived stress or mental health

reflecting traits over some time may better capture the stress reactivity that participants are taught in order to decrease the non-judgmental aspect of mindfulness meditation training. These characteristics may need to be captured by more prolonged assessments using ecological momentary assessment, or assessing stress reactivity using experimental stressors in a lab setting.

In summary, even though simple univariate statistics demonstrated some differences in baseline measures between responders and non-responders, classification accuracy using decision tree analysis was less than 70%.

Demographic variables were particularly not useful at predicting outcomes.

Improving the classification using other statistical or machine learning approaches or adding other predictor variables will be a useful future direction.

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Conflicts of Interest and Source of Funding.

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Chapter 5.

Discussion

The first paper in this dissertation discussed the complexity of the human stress system, including characterization of a stressor and the human physiology that responds to a stressor. There are several issues that are important especially from the systems science perspective that are reiterated or expanded here. 1) The human physiological system has many components that are altered by any stressor (see chapter 2, Figure 2.3). 2) The definition of a stressor event is not purely objective, i.e., there is no quantifiable metric of stressor severity that does not include individual aspects of the person since the effects of a stressor are highly dependent on an individual's perception. This subjective perception is dependent on issues such as learning, e.g., the effects of major trauma and conditioning, and genes or related systems, e.g., aspects of genetics, epigenetics, proteomics, and metabolomics, especially as related to neurotransmitter function and environmental reactivity. Event perception is also dependent on the specific environment in which the human exists although this could be considered an aspect of the stressor. For example the sound of a gunshot in a rifle range has a different significance than the same sound heard in a clothing store. A transient, i.e., not sustained, stressor impacts multiple human physiological measures and these transient state changes are often associated with physiological changes that are adaptive in nature. Perhaps the most well-known response to a stressor is the autonomic nervous system increasing heart

rate and blood pressure to allow for improved ability for “fight or flight”. However, if these responses are too sustained, then chronic hypertension or vascular disease may result. The cumulative or chronic effect of the changes to the human system resulting from repeated stressors is referred to as allostatic load by some [27]. Besides the more objective physiological changes, there are psychological changes sometimes referred to as “burnout” that have some degree of physiological correlates. These chronic changes to the person that may impact future responses to stressors can be thought of as trait changes to psychologists or parameter changes by systems scientists in contrast to more transient effects referred to as changes in state to psychologists or variables to systems scientists. The cost to system, i.e., the detrimental cost to the human of making these changes to their physiological system, depends on the magnitude and duration of the stressor (see Figure 2.4, Chapter 2).

In general, it is important to consider the degree of the stressor and the time course of the stressor when thinking about how the stressor effects humans. Some degree of stress may be important for the human so as to maintain adaptability and maximize performance. In terms of maximizing performance, the best athletic performances are often when a race or competition is particularly close. In terms of maintaining adaptability, making changes in the physiological system in response to a moderate stressor that is not sufficient to cause immediate harm may be beneficial. Exposure to an intermittent low level of a

stressor increases future ability to compensate to a future stressor without any decrement in utility because of adaptive changes to the physiological system and such system “learning” has been called hormesis [65]. For example, exposure to an intermittent low level of a toxin may allow a person to tolerate what would normally be a lethal dose and sometimes simple learning in response to a novel stressor may improve ability to learn to respond to future stressors. In general, acute mild or moderate stressors usually do not produce long-term negative effects although a significantly powerful acute stressor may actually push the brain dynamical system into a new, functional attractor basin with lower overall utility.

On the other hand, chronic psychological stress often produces changes in the system, such as a slower response to a future stressor or a higher potential for moving to a new lower utility attractor basin. As already mentioned, this has been referred to as *allostatic load*. Also, if a human is exposed to a “tolerable” dose of a stressor that results in return to the original high utility attractor basin, the outcome may be improved resilience. This balance between experiencing sufficient stressors to keep one’s physiological system adaptive or resilient versus experiencing declining health due to the cost of generating stressor responses is the reason for the inverted U-shaped effect of stress on function [277].

From a systems science perspective, behavioral and physiological measurements attempting to capture the degree of stress of a system need to go beyond static objective measurements. One needs to incorporate the dynamics of the physiological stress response system as well as measures of the environmental stressors and their perception. Understanding stress will require all of the interacting components from Chapter 2 Figure 2.3 to be measured empirically and described, at least partially. With regard to developing useful models of the systems dynamics of human stress physiology, there is a paucity of empirical data regarding the temporal aspects of the human stress response because it is difficult to acquire the human data. Nevertheless, acquiring and analyzing dynamical data will be important to better understand stress physiology since the timing and strength of feedback loops likely contributes to stress-related disorders and resilience to stressors. In addition to measuring stress responses over time, it may be useful to repeat administration of experimental stressors to better understand self-reinforcing loops. These systems science concepts and better measurement techniques will lead to improved understanding of the stress system, increased resilience of the human system, and better long-term health.

With the knowledge of the human stress system, the third chapter describes a clinical experiment involving 134 at least mildly stressed older adults to evaluate the effects of a stress-reducing intervention on psychological and physiological

markers. A randomized controlled clinical trial of a mindfulness meditation (MM) intervention was successfully implemented with a very low dropout rate. There were many outcome measures and there were very significant beneficial effects on many self-rated measures related to negative affect, stress, and mental health. The effect sizes of the various outcome measures were in the small to medium range with partial eta squared's ranging up to 0.13. The effect size reached a level above the minimal clinically important difference in the widely used mental health component score of the SF-36 health related quality of life measure. Despite the significant changes in mental health measures, there were no significant changes in the objective outcome assessments (i.e., not self-rated) of cognition, autonomic nervous system (heart rate and heart rate variability) and hypothalamic-pituitary-adrenal axis (cortisol).

Despite the negative findings concerning the objective measures in this study, it is still important to move beyond self-rated beneficial changes in stress and affect for two reasons. The first is to ensure that the benefits observed are not simply related to non-specific placebo or expectancy effects, and the second is to better understand the mechanism of MM benefits. Increasing our understanding the mechanism requires us to determine why there was a lack of changes in the objective measures of stress and cognition despite the significant improvements in self-rated measures of stress and affect. This discrepancy may relate to the

specifics of the particular intervention and/or outcome measurements, but also how one goes about assessing the stress system.

In terms of the intervention, it is possible the MM intervention was not as powerful as it could be but that wouldn't by itself explain the contrast in outcomes. Additionally, there is no way to assess the quality of meditation so it is possible that the meditation "dose" in this study was insufficient to induce cognitive or physiological changes. Of note, there was no relationship between simple minutes practiced and improvement in the outcome measures that did improve as a group.

There are many physiological measures related to stress described in Chapter 2 [224] and, while many of these may be sensitive to a short term stressor they may not be influenced by a longer-term stress-reducing MM intervention, MM. It is possible that the simple measures of autonomic nervous system and hypothalamic-pituitary-adrenal axis were not sufficiently sensitive. Other physiological changes not directly related to intracerebral processes such as telomerase and those referred to as allostatic load measures have mostly been reported to be sensitive to cross-sectional differences [141, 180-183, 212, 271] and may have similarly low sensitivity to an MM intervention. Assessing brain changes more directly in humans is possible with certain techniques, such as

EEG or MRI, but it is not possible to directly assess neurotransmitters as is done in non-human experimental subjects [278, 302].

Another possible reason for the discrepancy in outcomes may relate to the time course of the changes. It is possible that the intervention was not a sufficiently long duration. The outcomes may need to be measured over a much longer time frame or follow-up since physiological improvements related to stress improvement may not be so immediate (Visit 2 was at two months). For example, hair cortisol and hippocampal size reflect stress-induced changes over the long term but are not necessarily sensitive to acute or excessive transient responses [14, 166, 272]. The improvements related to meditation may primarily decrease responsivity to a stressor (resilience). The objective measures may need to measure resilience to stress either with experimental stressors or to consist of longer-duration assessments, e.g., using ecological momentary assessment over weeks or months. For example, cortisol on a typical assessment day may be less affected than the transient amplitude or the time course of cortisol changes in response to a stressor.

While possible explanations for the lack of changes in cognitive and physiological measures have already been discussed, it is becoming evident that more complex experimental and analytical approaches are needed to understand the MM-induced improvement in mental health and reductions in stress and negative

affect. Since reactivity to stress is a biologically complicated system and different people have different physiological sequelae to stress, researchers may well benefit from systems science methodologies to evaluate tightly coupled data taking into account the temporal aspect of the stressors and the varying time course of resulting changes in human physiology [119, 224].

Another approach to understanding the mechanisms by which MM moderates stress responses in human is described in detail in Chapter 4. In order to better understand the impact of stress on the human physiological system, it would be helpful to better understand the mechanisms of how a clinical intervention improves affect and perceived stress. More specifically, since MM was shown in Chapter 3 to improve outcome measures related to negative affect and perceived stress, the analysis in Chapter 4 determined what baseline personal factors would be able to predict the person's responsiveness to a MM intervention. It was hoped that understanding the predictors of who improved might shed light on the underlying mechanisms of MM benefits especially the puzzling fact that subjective measures improved but the objective measures did not (cognition, cortisol, heart rate and heart rate variability). Potential predictors for this study included demographic information (gender, age, income, years of education and exposure to life events) and selected baseline self-rated measures related to stress and affect.

The outcome chosen for the predictor analysis was the mental health component of the SF-36 health related quality of life measure since it had the largest effect size in the chapter 3 study and the adjusted mean difference compared to the waitlist control arm exceeded the minimum clinically important difference.

Analysis of the responders and non-responders to MM training revealed several significant differences in baseline measures. More specifically, those who improved from MM training had worse mental health prior to randomization than those who did not respond. The mental health measures that were different between responders and non-responders at baseline were the PANAS-negative, NEO-neuroticism, SF-36 Energy and Fatigue, and the SF-36 Mental Health Component, the latter being assessed at a later visit and was also used to define a responder. Machine learning using decision tree analysis to predict whether or not participant's mental health would improve following MM training had limited ability to correctly classify a participant as a responder or non-responder, with accuracy rates below 70% for almost all of the analyses and often below 60%, little better than a coin flip. The baseline measures that did appear in the decision tree classifiers were the ones already mentioned that were different at baseline using univariate statistics. The only other measures that occasionally appeared in the classifiers were the Life Event and expectancy measures. Mindfulness (non-judgmental), PANAS-positive, sleep quality, and self-efficacy were not useful at differentiating responder status. None of the demographic predictors including age, income, and gender were useful and they did not enter into the decision

trees. Additionally, none of these latter measures were significantly different in responder and non-responder groups using conventional biostatistics (all p's greater than 0.2) and at least one other study also found no relationship of outcomes to baseline demographic factors [289]. Besides the present study showing that those with the lower mental health improve more from a meditation intervention, other studies have also observed that those with worse mental health at baseline are more likely to demonstrate improvements from a meditation intervention [284, 285]. The fact that those who responded to the intervention had greater fatigue at baseline is of interest. It was previously shown that the SF-36 Energy and Fatigue subscore was sensitive to a mind-body intervention in two randomized controlled trials of 6 months of yoga compared to control, one in a group of 69 people with multiple sclerosis [288] and one in a group of 135 healthy older adults.[242].

Expectancy has an impact on many outcomes, especially on self-rated outcomes [115, 267]. Having only a wait-list control implies that some benefit of MM compared to wait-wait-list in this, or any study, may be related to placebo effects [115]. If this were the case, there would be two types of response to the MM intervention confounding the analysis, i.e., placebo responsiveness predicted by certain variables such as expectancy and responsiveness to the MM intervention predicted by other variables such as mental health. Regarding expectancy effects among patient with cancer being randomized to meditation or one of two other intervention groups, the mindfulness intervention was the most preferred

program [291]. However, those randomized to their preferred intervention improved more over time on quality of life regardless of actual intervention type. Women with greater psychological morbidity at baseline showed greater improvement in stress symptoms and quality of life if they received their preferred vs non-preferred program [291]

There were several limitations to this study. From a machine learning perspective, the number of observations (participants) is small. To potentially ameliorate this concern, the analysis was limited to nine predictors so that there would be 10 observations per variable in the training set. Decision tree analysis might have slightly benefited from methods such as ensemble learning or AdaBoost methods [298]. Additionally, decision tree analysis may not be the best machine learning approach for this type of data [299]. Also, adding costs of allocation and misallocation to the decision analysis might make the analysis more interpretable but at this level of classification accuracy it was not felt to be worthwhile.

A more general issue with predictor analysis in clinical trials is that responder status is in part related to regression to the mean especially since many of the predictor variables are correlated to the SF-36 MHC score. Thus, those with lower SF-36 MHC will be more likely to improve and many of the self-rated predictors correlate with the SF-36 MHC (e.g., SF-36 energy, NEO-neuroticism,

PANAS-neg). One prior study did suggest that regression to the mean is not the only issue .[113] as well as additional data from the dissertation study.

Participants in the wait-list control arm of this dissertation study had no major changes in their measures of stress and negative affect during the wait-list period (Visit 1 to Visit 2) also suggesting that regression to the mean is not the only issue. An additional limitation of the study is the lack of variability in the study sample demographics consisting of mostly highly educated women in a relatively narrow age range (50-85 years old) may limit both the quantitative analysis as well as the generalizability. The prevalence of women is common in mind-body intervention studies. Broader inclusion criteria for the next study would be helpful.

Even though simple univariate statistics demonstrated some differences in baseline measures between responders and non-responders, achieving a useful classification accuracy using decision tree analysis was not achieved. Improving the classification using other statistical or machine learning approaches or adding other predictor variables will be a useful future direction. This could potentially help assess interactions of the variables that may need to be better captured. Machine learning is a broad field [300, 301] and other machine techniques may be better than decision tree analysis for this data Khondoker, 2013 #6282}. Additionally, it is likely that these particular predictor variables were not capturing important dynamic properties of a person that might relate to responsiveness to an MM intervention. Stress reactivity rather than simply perceived stress or

mental health reflecting traits over some time may better capture the stress reactivity that one is taught to decrease in the non-judgmental aspect of mindfulness meditation training. These characteristics may need to be captured by more prolonged assessments using ecological momentary assessment, or assessing stress reactivity using experimental stressors in a lab setting.

In summary, maintaining cognitive health with aging is an important public health issue given the incidence of age-related cognitive decline as well as it being of personal concern to most adults. Stress is known to effect cognitive health at least in situations deviating from the population average such as major depression, post-traumatic stress disorders, and neuroticism. It is unclear if milder mental health problems - the target in this study - actually produce significant cognitive changes, and it is unclear if a stress- reducing intervention in such people who may be functioning close to their maximal level of performance would be of any benefit to their cognitive health. However, the study did demonstrate that self-rated mental health significantly improved from a MM intervention in mildly stressed older adults, adding another population to the evidence basis for MM.

There are a number of future research directions that were pointed to by this study. One future research direction having a clinical implication is to define the threshold of stress a person is experiencing in order to better predict who may

benefit from an MM intervention. Another future research direction is to optimize the intervention itself. The MM training sessions in this study were one-on-one sessions adapted from the widely used and standardized Mindfulness-Based Cognitive Therapy. It is possible that making the intervention more easily available and potentially individually tailored by converting it to an internet delivery would be better.

More importantly regarding the intervention itself, another future research direction will be to focus the intervention to foster non-reactivity to events. MM has two main components: focusing attention to the current moment and being non-judgmental. The non-judgmental component is essentially decreasing stress reactivity and an MM intervention focused on that aspect may be preferred. The other MM component, attention to the current moment may not decrease stress reactivity. For example, someone with PTSD who focuses on the experience of an increased heart rate or sense of stress when around some external environmental trigger will not experience improved clinical symptoms and may simply self-reinforce their being trapped in a non-optimal attractor basin. An additional research direction regarding the intervention itself would be to develop more objective markers for meditation quality, specifically the attention to the current moment or the non-judgmental/ non-reactivity to stressors. While there were clear and significant MM benefits in this study on self-rated measures related to affect, stress, and mental health, it is still unclear how these changes would translate into physiological effects. Thus, another future direction for

understanding the benefits of a stress-reducing intervention such as MM would be to develop better physiological markers for stress, in particular to capture the dynamics of the person's response to stress, i.e., their resilience to stress. This could include ecological momentary assessment over longer time periods to gain a better understanding of the variability of the stress markers. Another approach to better understanding resilience to stress would be to utilize an experimental stressor in the lab setting. Finally, a less well-defined but always present future research direction is the development of better models and better quantitative analysis approaches to the multivariate but dynamically limited human empirical data that can be practically collected.

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