7-1-2021

Sudarshan Kriya Yoga and Alteration in Depression Severity and Default Mode Network Connectivity

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SUDARSHAN KRIYA YOGA AND ALTERATION IN DEPRESSION SEVERITY AND DEFAULT MODE NETWORK CONNECTIVITY

A Thesis Presented to
The Faculty of the Yale School of Medicine
Yale University

In Candidacy for the Degree of
Master of Medical Science

July 2021

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List of Abbreviations

MDD Major Depressive Disorder
RCT Randomized Controlled Trial
MBI Mindfulness-Based Intervention
MBSR Mindfulness Based Stress Reduction
MBCT Mindfulness Based Cognitive Therapy
BDI-II Beck Depression Inventory, Second Edition
HAM-D17 17 Item Hamilton Depression Rating Scale
DSM-IV, DSM-V Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Fifth Edition
fMRI Functional Magnetic Resonance Imaging
FC Functional Connectivity
rsfcMRI Resting State Functional Connectivity Magnetic Resonance Imaging
PCC Posterior Cingulate Cortex
amPFC Anterior Medial Prefrontal Cortex

Abstract

Major depressive disorder is one of the most common and burdensome psychiatric disorders. Many individuals still experience symptoms despite pharmacological treatment. Breathing techniques have shown potential for stress, depression, and anxiety reduction. A second promising treatment are mindfulness-based interventions, which have been shown to effectively decrease depression with fewer side effects than pharmacological agents. Both interventions are accessible via remote instruction. This study will investigate the effect of Sudarshan Kriya Yoga breathwork on depression symptoms. Using a prospective, randomized controlled trial, subjects will receive Sudarshan Kriya Yoga, Mindfulness Based Stress Reduction, or standard care for 8-weeks. We will measure changes in depressive symptoms using two validated depression inventories and will examine their effects on selected brain regions using resting-state functional magnetic resonance imaging. These results may guide an integrative approach for depression, expanding current options through a low-cost, low-risk, and accessible behavioral intervention adjunctive to concurrent pharmacological treatment.

CHAPTER 1: INTRODUCTION

1.1 Background

1.1.1 Depression Epidemiology and Recurrence

To date, more than 264 million people suffer from major depressive disorder (MDD), accounting for 22.8% of the global burden of disease.[1] MDD is pervasive across age groups, ethnicities and socioeconomic statuses.[2] Beyond the potential to be disabling psychologically, depression is associated with reduced quality of life, greater health comorbidities, and excess mortality.[3,4] Further, there is a high likelihood of depression recurrence following completion of traditional pharmacological approaches.[5]

1.1.2 Clinical Definition and Diagnostic Criteria

MDD is clinically defined in patients with a history of at least one major depressive episode without mania or hypomania. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), a major depressive episode consists of five or more of the following symptoms, one of which must be either depressed mood or anhedonia: insomnia or hypersomnia, appetite decrease or increase, unintentional weight loss or gain, psychomotor retardation or agitation, fatigue, poor concentration, excessive thoughts of worthlessness or guilt, and recurrent thoughts concerning death or suicide.[6] The symptoms must all be present within the same two-week period and reflect a significant change from prior baseline functioning. Lastly, the diagnosis of MDD is reached when excluding other disorders such as delusional disorder

or schizophrenia, and the symptoms must cause a significant impairment in social, occupational, or other areas of functioning.

1.1.3 Depression: Goals of Treatment & Initial Treatment Options

When considering the goals of treatment, it is important to distinguish two concepts: response and remission. Based on a clinician rated depression scale, response is considered improvement ≥ 50% from baseline depression rating score, while remission is achieved once the overall depressive syndrome is concluded. Initial treatment aims for complete depressive symptom remission and return to baseline functioning.[7,8]

While both psychotherapy and pharmacotherapy are validated options for treatment, most often antidepressants are chosen as first line management for MDD.[9-12] Selective Serotonin Reuptake Inhibitors (SSRIs) predominate and are the most widely prescribed class of antidepressants.[9,13] One reason for their frequent implementation is that antidepressants have been shown to be effective in multiple meta-analyses of randomized controlled trials over years of research[14-17] and thus accepted into practice guidelines.[18,19] From a patient perspective, contributing factors such as cost, comorbidities, and psychosocial stressors must be taken into account when considering these two treatment options.

Although over a thousand randomized clinical trials have been conducted with antidepressants, there are concerns regarding comprehensive study design elements and antidepressant efficacy, safety and tolerability.[20] Improper interpretation of statistical significance, publication bias[21], manipulated study design, selection bias of study populations, short term follow-up which excludes discussion of potential long term adverse effects, and focus on clinically non-relevant outcomes have the potential to

construct a false sense of security regarding antidepressant effectiveness and tolerability. Furthermore, SSRIs have side effects such as sexual dysfunction, lethargy, drowsiness, nausea, weight gain and alteration of normal sleep pattern which reduce compliances.[22] Conversely, the antidepressant can be changed to a different class, which prolongs the time for the new drug to reach effectiveness and thus the amount of time it takes for the patient to achieve response and remission.

Patients may discontinue their antidepressants suddenly following remission which carries a risk of relapse and discontinuation syndrome.[23] These withdrawal effects may appear within hours to days after cessation, and include dizziness, gastrointestinal complaints, lethargy, flu-like symptoms, irritability and anxiety.[24] By extension, these distressing symptoms may result in unnecessary and costly testing if not recognized as symptoms of discontinuation.[25] These findings illustrate the necessity of exploring whether we can supplement antidepressant pharmacological therapy in order to improve antidepressant response, limited adverse effects, and achieve remission.

1.1.4 Introduction to Sudarshan Kriya Yoga

Sudarshan Kriya Yoga (SKY) is a type of yogic breathwork consisting of three types of breath: ujjayi, bhastrika, and Sudarshan Kriya, in addition to a brief chanting component.[26] There is a rest period of approximately 20 seconds following each of the four stages of breathing. Ujjayi, also called “victorious breath”, consists of 2-4 cycles per minute (cpm) of nostril breathing with a slight constriction of the laryngeal muscles to produce a shallow, ocean-like sound when breathing. Each cycle consists of 4 count inspiration, 4 count end-inspiration hold, 6 count expiration, and 2 count expiration hold, complemented with hand placement on the lower belly, ribs or upper back. The second

component called Bhastrika or bellows breathing is a forceful technique where air is actively inhaled and exhaled with the use of abdominal muscles at approximately 15-20 cpm. Next, participants typically chant the word “om” three times on a long exhale with a 15 second rest period after each chant. The last breathing component of SKY is Sudarshan Kriya, which unlike the first component has no end expiration or end inhalation breath holding. Inhalation and exhalation phases are equal in duration and no airway resistance is used, unlike ujjayi. Sudarshan Kriya has three different rates of breathing: slow (8-14 cycles per minute, cpm), medium (30 cpm) and rapid (150-180 cpm) (See Appendix A). The number of breaths and duration of cycles differ between in class sessions and at home individual practice. This session typically closes with kriya, a slow, steady set of 8-10 slow cycles with a 5-minute period of rest in the supine position to prevent dizziness and lightheadedness when standing up.

Different types of yoga incorporate mindfulness meditations, breathwork and physical postures or asanas. The protocol for SKY in our proposed study will not require physical movement, which makes it accessible to most ability levels. SKY has been utilized as an intervention for anxiety, stress and depression.[26] The exact mechanism through which breathwork achieves beneficial effects is unknown, but some studies highlight its influence on cardiovascular parameters, autonomic variability, and cerebrovascular hemodynamics.[27-29] SKY holds promise as an adjunctive treatment option for MDD given its ease of use, accessibility, lack of adverse effects, as well as potential long-term benefits even after concluding the intervention.

1.1.5 Introduction to Mindfulness Based Stress Reduction

A widely accepted operational definition of mindfulness-based interventions (MBIs) consists of two core concepts. Self-regulation of attention on the current moment complements an overall view of openness and acceptance regarding the present moment which includes any intrusive or distressing thoughts, emotions or memories.[30] Attention is self-regulated and maintained in a non-ruminating and nonreactive way, which is beneficial for the depressed patient population, as rumination is a prevalent symptom.

Mindfulness Based Stress Reduction (MBSR) was the first MBI to gain empirical support.[31] The three components of MBSR are full body scan, sitting meditation, and Hatha yoga. The combination of mental and physiologic components promote stability of mood, lessen reflexive rumination, and potentially extend periods of depressive remission in a depressed patient population.[32,33]

1.1.6 Introduction to the Default Mode Network

The default mode network (DMN) is an interconnected neurological circuit shown to be active during times of self-referential thought and non-task-based states.[34] It is made up of discrete areas of the brain: a central midline core made of the posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC) which communicates with two subnetworks: the dorsal medial prefrontal cortex (dMPFC) subsystem and the medial temporal lobe (MTL) subsystem.[35] The DMN has also been associated with self-reflection on one's own emotional state, which would support its relationship with psychological disorders and over time with depressive rumination.[36,37] The DMN is the brain's intrinsic, ongoing activity that is active when participants are not focused on the outside world, such as mind wandering.[38] The DMN has been an area of interest in

depression because depressive, self-focused thoughts may correlate with the baseline within-network DMN hyperconnectivity that is uniquely seen in depressed patients. [39]

1.2 Statement of the Problem

MDD is a disabling disease typically treated with pharmacological therapy which has modest short-term benefit and variable long-term effectiveness. Despite use of first line pharmacotherapy, many individuals still suffer from depressive episode recurrence and do not achieve remission. There is a clear need for interventions beyond pharmacology, including further validation of Mindfulness-Based Interventions such as Mindfulness Based Stress Reduction, and other non-pharmacological interventions. Sudarshan Kriya Yoga, with its emphasis on breathwork, has the potential for effectiveness as an adjunct therapy to antidepressants. Behavioral adjuncts may help to prevent escalation to high intensity therapies (such as one to one psychological therapies) and avoid further financial, emotional, and psychological burden within the patient population.

1.3 Goals and Objectives

The primary aim of this study is to evaluate the antidepressant effectiveness of Sudarshan Kriya Yoga as adjunctive treatment for MDD in comparison to Mindfulness Based Stress Reduction and solely pharmacologic treatment. The secondary aim is to investigate potential change in functional connectivity within the DMN in mild to moderately depressed patients on stable pharmacological therapy who receive SKY or MBDR as adjuvant therapies.

1.4 Hypothesis

In this study, it is hypothesized that there will be a statistically significant difference in depressive symptoms in subjects aged 18-65 years old with mild to moderate depression on stable antidepressant pharmacological therapy following an 8-week SKY intervention as adjunctive treatment, as measured through the 17item Hamilton Depression Rating Scale (HAM-D17)[40] (see Appendix B) and Beck Depression Inventory, Second Edition (BDI-II)[41] (See Appendix C) compared to a group using MBSR as adjunctive treatment alongside pharmacologic therapy, and a third group continuing their pharmacological treatment only.

To address the second aim, it is hypothesized that resting state functional connectivity MRI (rsfcMRI) scans will show a change in DMN functional connectivity (FC) as measured through BOLD signal changes when comparing baseline imaging obtained prior to SKY intervention to imaging acquired post-intervention. Definitely need to define DMN in a background section or reader will no know what this means.

1.5 Definitions

Resting state (fMRI scanning condition): the participant is not performing a task or responding to a stimulus. Instead, he/she will be awake but with eyes closed, not thinking about anything in particular.

Functional connectivity: temporal associations of synchronous neural activity between anatomically separate brain regions either at rest or during a task

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CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

2.1.1 Literature Search

A thorough literature search was conducted by means of PubMed, Scopus, and The Cochrane Library from December 2020-July 2021. Studies, meta-analyses, and reviews relevant to the proposed study were initially based on perusing titles and abstracts. A final search was completed on July 6, 2021. Key terms used in each data base pertinent to the psychological disorder of depression included *major depression, MDD, major depressive disorder, unipolar depression, depressive disorder, depression,* and *depressive.* Studies utilizing yogic breathwork were also searched for by alternating terms such as *pranayama, Sudarshan Kriya Yoga, SKY, breathwork, controlled breathing,* and *yoga(ic) breathing.* Terms used to identify papers based on mindfulness interventions included *mindfulness, mindful, meditation, mindfulness-based intervention, MBI, MBSR, mindfulness-based stress reduction,* and *stress reduction.* Lastly, alternative terms for the default mode network included *resting state network, DMN, default network, resting state, resting state connectivity, functional connectivity,* and *functional brain network.* We also used terms relevant to the anatomical aspects of the default mode network such as *posterior cingulate cortex, PCC, cingulate cortex, medial prefrontal cortex,* and *prefrontal cortex.* The aforementioned search terms were used in various combinations, combining categories using *and/or* functionalities.

Literature returned from the initial search (n=374) included prospective studies, retrospective studies, clinical trials, randomized controlled trials, meta analyses and systematic reviews. International studies were included in the review, but the search was limited to the English language only. We also used articles from reference lists of the studies that were selected after our initial search.

2.2 Sudarshan Kriya Yoga and Mindfulness Based Stress Reduction

2.2.1 Sudarshan Kriya Yoga Interventions in Depression

Sudarshan Kriya Yoga (SKY) has been shown to lessen the severity of stress, anxiety, and depression. A prospective, randomized controlled trial (RCT) focused on severe depression fulfilling DSM-IV criteria and had three distinct treatment arms: a 30 minute SKY session once a day versus imipramine versus bilateral electroconvulsive therapy (ECT) three times per week.[1] In order to isolate the effect of SKY breathwork, only the three breathwork phases- ujjayi, bhastrika and Sudarshan Kriya- were taught without mindful or relaxation techniques. The SKY arm showed a statistically significant 67% remission rate (defined as having a Hamilton Depression Rating Scale total score < 7), which is particularly impressive given the severity of the patients' depression. At the end of 4 weeks, SKY was superior to imipramine therapy and did result in lower depression symptom severity.

A majority of studies taught SKY comprehensively using breathwork with guided meditation and stress relieving skills. An intervention program in the United Kingdom recruited individuals with mild to moderate depression and anxiety disorders who were taught in four weekly, one-hour sessions with a certified SKY instructor.[2] Intention to

treat analysis showed a statistically significant reduction in self-reported depression symptoms by 22% and reduction in anxiety by 30% ($p<0.001$). All statistically significant differences remained when performing subgroup analysis based on age groups, males versus females, and medication use. Another clinical trial utilized SKY breathwork with chanting in addition to weekly self-help groups and mindfulness tactics for 6 months in subjects with a primary DSM-IV diagnosis of a Mood disorder, including depression.[3] In the depressed population, patients with and without antidepressant use both showed very low to absent depression symptoms following completion based on the clinician rated Hamilton Rating Scale for Depression (HAM-D 17) and patient completed Zung Self-Rating Scale for Depression. The use of antidepressant medications did not seem to significantly affect scores, which limited possible confounders. Given that medicated subjects included in Group 1 were on the same dose for the past 6 months, the medication's effect reached a steady plateau. Thus, SKY could be seen as the compelling factor that propelled improvement in depression which remained at 6 month follow-up.

A randomized waitlist-controlled trial utilized an 8-week intervention of SKY breathwork with yoga, mindfulness meditation, and stress education in treatment resistant major depressive disorder (MDD) patients.[4] Treatment resistance was defined as persistence of a non-psychotic, depressive episode despite ≥ 8 weeks of antidepressants. Intention to treat (ITT) analysis showed that participants had an average reduction in HAM-D17 total score of 9.77, which improved more than waitlist control (0.50). The study had high completion rate at 77% despite significant time requirement with many patients having school or work commitments during the day. To the researcher's

knowledge, this was the first study to show SKY as an effective and highly tolerable adjuvant measure for treatment resistant depressed patients.

2.2.2 Mindfulness Based Interventions in Depression

It is thought that practices which center around mindfulness, termed mindfulness-based interventions (MBIs), alleviate intense emotional states such as cyclical rumination common in depression.[5] Clinically applied MBIs within the field of mental health include Kabat-Zinn's mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT). In a meta-analysis of MBIs for psychiatric disorders, it was found that MBIs were superior to no treatment and were equivalent to evidence-based treatments such as antidepressants.[6]

A different meta-analysis evaluated twelve RCTs (n=578) utilizing MBIs such as MBSR for participants meeting DSM-IV criteria for MDD or an anxiety disorder compared to waitlist and active controls.[7] All studies had a primary outcome of change in symptom severity, measured through self-report and clinician rated questionnaires including the HAM-D17. Random effects models showed that there was a post-intervention between-group difference in favor of MBIs on primary symptom severity with a medium effect size that was statistically significant ($p<0.01$). Effects of MBIs on depression symptom severity replicated findings of a previous meta-analysis.[8]

One of the most comprehensive reviews analyzed 209 trials of MBIs among 12,145 patients with varying psychological disorders, ages, and genders.[9] This meta-analysis concluded that MBIs were more effective in lessening the severity of both psychological and physical symptoms when compared to waitlist, psychoeducation, supportive psychotherapy relaxation training and imagery, and suppression techniques.

When analyzing the selected studies that targeted depression, the mean effect size on depression was moderately strong for 5 pre-post studies and moderate for 8 waitlist-controlled studies. Patients with baseline mild to severe depression all showed reduction of depression severity to mild and moderate levels respectively post-treatment based on the BDI-I and BDI-II. Treatment effects remained stable over follow-up periods ranging from 3 weeks to 3 years. These findings mirror those of a prior meta-analysis[8], which concluded that mindfulness-based therapies showed a clinically significant large effect sizes that maintained through a period of follow up.

A one-month long RCT used somatic relaxation training as an active control comparing the effects of mindfulness meditation (MM) modeled on MBSR protocol.[10] It was hypothesized that both MBSR and somatic relaxation training would be beneficial in reducing overall stress, but only the mindfulness intervention would reduce distracting and ruminative thoughts. This study was included within our literature review because rumination is a key symptom in depression. The protocol did match MBSR in its use of body scan, sitting meditation, and Hatha yoga. At the conclusion of the study, unique to only the MM group was the significant pre-post decreases in both distractive and ruminative thoughts/behaviors based on the Daily Emotion Report, a self-report questionnaire. Thus, the MM based on MBSR showed a unique ability to lessen rumination and distraction, common symptoms of depression.

2.3 Feasibility and Efficacy of Internet Based Interventions

In light of the current COVID-19 pandemic with understandable social distancing and restrictions in sizes of gatherings, technology may be the greatest ally in continuing

mindfulness-based interventions. In the place of face-to-face MBIs, clear direction and insight can still be achieved through the use of computer, smart phone, or tablet-based interfaces and remote, online programming. Furthermore, it is adaptable to both individual therapy and group therapy without posing a health risk.[11]

The proposed study's focus on depressed individuals is pertinent as well. COVID-19 can have emotional, mental and physical health consequences as it interrupts daily living.[12] A population-representative survey study showed that the prevalence of depression had increased more than three-fold during the pandemic. Furthermore, more severe depressive episodes during this pandemic may elevate drop-out rates from treatment secondary to significant loss of motivation and debilitating apathy common in depression, leading to inconsistent attendance.

Of note, the same survey showed that lower income during COVID-19 was associated with a greater risk of depression, showing the disproportionate effect when having less than $5000 in savings account was correlated with a 1.5 fold increased odds of depressive symptoms, or 50% greater risk. As a result, resource limited communities are a key patient population to evaluate. And yet, they may be excluded from in person studies due to factors related to health disparity such as work schedules, child care, and transportation costs. Therefore, it is more likely that in-person studies automatically exclude large segments of the population. As a result, incorporation of internet-based interventions may strengthen outreach and incorporation of those vulnerable patient populations.

In one meta-analysis of 15 RCTs studying the relationship of online MBIs with measures of mental health and well-being, online MBIs including MBSR had a beneficial

effect on depression, anxiety, mindfulness and well-being.[13] This meta-analysis was the first to show that online MBIs strengthened aspects that pertain to greater quality of life, including well-being and mindfulness with a significant small effect size. A randomized control pilot study utilized an internet-based mindfulness program over 8 weeks to improve stress in adults without psychological disorders.[14] Researchers adapted strategies from MBSR, including body scan, mindfulness meditation, and sitting meditation. Individuals who completed the mindfulness meditation course had a mean Perceived Stress Scale score of 14.44 (±5.86) compared to a mean score 23.73 (±9.95) at the beginning of the course, which was a statistically significant change ($p<0.001$) that remained at 1-month follow-up. The pre-post effect size was 1.57, which is higher than face-to-face MBSR and cognitive therapy courses ranging from 0.52 to 1.19 as mentioned within the study. While limitations include lack of a control group and lack of assessment of anxiety and depressive symptoms specifically, this study showed that online mindfulness courses seem to achieve similar results to face-to-face therapies.

Another RCT evaluated the efficacy of unguided internet-based mindfulness treatment for anxiety disorders.[15] The mindfulness treatment group protocol consisted of 96 audio modules centered on sitting meditation, body scan, and mindfulness movement to be performed 6 days per week for 8 weeks. This was compared to an online discussion forum control group. Intention to treat (ITT) analysis showed that the mindfulness group had a larger improvement in anxiety and depressive symptoms as well as insomnia from baseline to after intervention. The BDI-II showed improvement in the mindfulness group more so than the control group. When considering the implementation of internet-based

mindfulness therapies in both clinical and nonclinical populations, there is support for efficacy and feasibility of internet-based mindfulness therapies to improve mental health.

2.4 Depression and the Default Mode Network

2.4.1 The Neurobiology of Depression

Depressed individuals tend to focus most of their attention on negative stimuli and excessively ruminate.[16] The cognitive model of depression states that depressive symptoms arise from and are sustained by maladaptive thinking processes such as attention bias and dysfunctional attitudes. The neurobiological model of depression coordinates these cognitive maladaptations with brain functional connectivity and anatomy.[17] These brain regions can be identified at baseline using fMRI, which also has the potential to assess treatment outcomes and effects in various trials.[18]

Seeking to understand the affective aspects of self, researchers had healthy subjects judge a series of personality traits and how that described themselves from “not at all like me” to “very much like me” on a 4 point Likert scale.[19] A voxel-wise analysis of variance (ANOVA) between valence of traits and relevance of rating showed that both the mPFC and posterior cingulate cortex (PCC) were preferentially activated during fMRI when subjects were presented with self-relevant material, regardless of positive versus negative valence. A prior fMRI study also found peak mPFC activity when all subjects without psychological disease made self-referential judgements versus answering general semantic knowledge questions.[20] While Johnson’s study (2002) showed statistically significant mPFC activity with regards to self-relevant knowledge (p=0.05), Moran’s (2004) study extended those findings when subjects showed greater

mPFC activity specifically with traits that were akin to their own personality, possibly indicating increased self-referential thought or focus. Increased self-focus is a core feature in the pathology of MDD according to cognitive theory, and it has been shown to extend and worsen the severity of depressive episodes by perpetuating depressed thought and mood.[21,17,22]

2.4.2 The Neurobiology of the Default Mode Network

The Default Mode Network (DMN) is defined as a network of brain regions that show coherent activity during a resting state and increased activity when individuals are focused on their internal state, such as self-referential thought.[23] Shulman and colleagues (1997) first established the presence of the DMN in a meta-analysis of 9 PET-scan studies, which demonstrated an interconnected resting state network with task activity attenuation.

Over many subsequent studies, the DMN has been established to be involved in many neurological disorders including major depressive disorder.[24-27] Relevant to the proposed study, Gusnard and colleagues (2001) found that in healthy subjects, the medial prefrontal regions were preferentially associated with an increase in neural activity during internally cued conditions.[28] As a result, these regions must play a large role in introspection. The anatomical and functional network of the DMN was further mapped in a series of eloquent studies undertaken by Andrews-Hanna and colleagues using functional connectivity MRI (fcMRI).[29]

In an initial experiment, the authors found evidence for two distinct sub-networks working in a cohesive manner and interacting with a core region.[29] These two networks were termed the dorsal medial prefrontal cortex (dMPFC) subsystem and the medial

temporal lobe (MTL) subsystem, distinct and separate as they had a correlation of near zero. The anterior medial prefrontal cortex (amPFC) and PCC were found to make up the common core of the DMN as they both showed the highest betweenness-centrality as defined by their statistically significant activity correlations (p<0.001).[30] In the second experiment, regions within the dMPFC subsystem were selectively active in the Present-Self condition, while the MTL subsystem showed much higher engagement in the Future-Self condition. The PCC-amPFC core region demonstrated strong activation during both present and future-self conditions, serving as a thorough way for the two subsystems. Therefore, the dMPFC focuses on the current, present mental state of one's self and others, while the MTL subsystem focuses on future related self-reference, and the core allows for coordination of both systems.

2.4.3 Major Depressive Disorder and the Default Mode Network

Elevated DMN functional connectivity (FC) has been shown to be a reliable neural marker of MDD.[25,31] On baseline imaging, depressed subjects exhibit the unique finding of DMN hyper-connectivity.[26,27] A meta-analysis compiled 27 studies analyzing neurological activity using resting state functional connectivity MRI (rsfcMRI).[27] The brains of depressed patients had significant hyperconnectivity within the DMN. Interestingly, there was a greater likelihood of hyperconnectivity in unmedicated MDD patients between the DMN seeds and the hippocampus (likelihood ratio=6.01, p=0.09). This suggests that higher activity within the DMN reflects greater severity of depressive symptoms. These findings support the neurocognitive model in which brain network dysfunction is highly correlated to a persistent, negative mood such as in MDD.

One of the largest, multi site fMRI studies on MDD used a dynamic network-based approach, evaluating the resting state fMRI data from 460 patients with DSM-IV criteria of MDD and a HAM-D17 score ≥ 8.[32] Following ANCOVA, the PCC and mPFC showed significant alteration in activity compared to healthy controls. This increase in activity was consistent with prior studies, which suggest a relationship between aberrant FC in the DMN and self-reflective, ruminative thinking contributing to depression severity.[27,33] Rumination is a core feature of depression and consists of persistent, internally directed thought.[21] Our proposed study will investigate not only baseline activity of the DMN in depressed individuals, but also following additional interventions to see if that baseline hyperactivity is modifiable.

A review paper discussed whether observing change in DMN FC can serve as an effective tool for depression diagnosis and lead to more successful interventions.[34] All the studies considered consistently emphasized the DMN as a key factor contributing to MDD and its relationship with depressive symptoms like rumination and excessive self-referential thought. Another early fMRI study demonstrated that individuals with MDD had an elevated resting state subgenual cingulate and DMN FC while resting quietly as compared to health controls.[35] Within group correlational independent component analysis (ICA) demonstrated enhanced subgenual FC associated with greater lengths of depressive episodes, reinforcing a possible relationship between brain FC and severity of psychological disease. Our study will expand upon these findings by analyzing fMRI scans with change in depression symptoms following interventions.

Researchers quantified resting state connectivity within three distinct resting state brain networks, including the DMN, in unmedicated patients with MDD (HAM-D17 ≥

18) compared to non-depressed controls (HAM-D17 ≤ 7).[36] Patients suffering from depression had enhanced connectivity within the DMN and ANCOVA analysis using sex, age and education as covariates and did not contribute to the model despite significant between-group differences. This study once again implicated increased resting-state DMN FC as indicative of more self-focused thinking and strengthened the potential to use FC as a marker for depression severity both before and after treatment, as in our planned study.

2.4.4 Rumination and the Default Mode Network

Depressive rumination is defined as a persistent, self-reflective, and unintended focus on depressive distress symptoms, causes and outcomes. It is reliably associated with MDD with both adaptive and maladaptive components.[21,37] The extent of rumination is even predictive of future depressive symptoms over time and risk of relapse.[38,39] A narrative review of 94 studies of resting state brain network function in MDD found that the DMN reliably showed connectivity alterations when compared to individuals without mood disorders.[40]

Berman and colleagues used seed-based fMRI analysis with the PCC and mPFC to evaluate rumination and the strength of association with DMN.[41] Again, DMN connectivity with those brain regions was related to rumination ($p < 0.005$). To rule out possible contributions from the depressive subscoring used in the Ruminative Responses Scale (RRS), focused analysis of connectivity scores from the brooding component of the RRS still resulted in a positive relationship ($r = 0.19$, $p < 0.05$). The main effect of group did not drive the correlation between RRS scores and PCC FC, just as it was when using the two-sample t-tests for the functionally defined regions of interest. The study was

strengthened through its consistent fMRI analytical protocol with two well established core brain regions of the DMN.[29]

One meta-analysis of 14 studies explored the relationship between brain regions and rumination within neuro-imaging studies, which was previously lacking.[42] Prior conclusions had been unclear, possibly due to inconsistency in sample sizes, various demographic variables, and varied individual clinical features of subjects. What had been clear throughout prior studies though was a unique relationship between rumination and self-referential processing as signified through increased activity of cortical midline structures in depressed individuals.[43-45] The PCC and amPFC demonstrated highest activation after rumination induction. Hyperactivation specifically within the DMN core and dmPFC subsystem was associated with introspection and ruminative thought.[46]

This meta-analysis also helped to clarify the temporal aspect of ruminative thoughts.[42] The DMN core regions (amPFC and PCC) and dmPFC subsystem were persistently activated when ruminating, while the MTL subsystem was not activated. According to Andrews-Hanna (2010), the MTL subsystem is associated with autobiographical recall while the dmPFC focuses on thinking about one or another person's current mentation. The findings support that rumination in depressed subjects center negative thoughts regarding their own present mental states and environment rather than the future. Therefore, mindfulness-based interventions which focus on the present moment and associated emotions may be of benefit for those with MDD.

2.4.5 Other Associated Variables

Alterations in DMN FC are also present in those who are at high risk to develop depression[47,48] and are present in depressed individuals regardless of age.[49,50] A study

used fMRI to evaluate 111 individuals aged 11-60 years old at high and low familial risk for depression, a part of a three-generational longitudinal cohort study of familial depression that began in 1982.[47] If first generation subjects did have MDD, then subsequent generations were considered high risk. ICA showed that individuals at high risk had increased DMN connectivity, especially within the PCC, precuneus, and mPFC. Individuals at low risk showed no areas of increased activity within the DMN. In another study, resting state FC MRI evaluated connectivity changes within first episode, treatment naïve depressed individuals.[48] Combined regional-wise FC analysis showed aberrant connectivity between the mPFC and PCC. Both regions are associated with aberrant executive control and emotion processing.[51]

Depression can also occur in the extremes of age. A case-control study examined FC of 306 school aged children aged 8 years or older with a history of preschool onset depression (PO-MDD).[49] Using the PCC as seed region, rsfcMRI scans showed that children with known PO-MDD had significantly increased connectivity between the PCC and cortical midline regions such as the mPFC. This study replicated findings from other studies in adults with MDD.[36,41,42] A different study focused on a population of unmedicated individuals aged 60 or older with MDD before and after escitalopram.[52] There was no correlation between DMN FC and treatment response based on change in MADRS scores. However, at baseline, late life depressed patients did exhibit heightened FC within the DMN PCC seed region and the left precuneus. Across the ages, there is a consistent, unique finding of increased resting state DMN FC within depressed individuals. Our study incorporates DMN FC as a secondary outcome to evaluate potential change through various interventions, pharmacological or otherwise.

2.5 Nonpharmacological Interventions and the Default Mode Network

2.5.1 Sudarshan Kriya Yoga and Default Mode Network Functional Connectivity

Despite a focused and exhaustive search on various databases, no articles were found linking the DMN with SKY specific interventions.

2.5.2 Mindfulness Based Interventions and Default Mode Network Functional Connectivity

As described previously, the DMN is a functionally distinct network of brain regions with coherent activity at rest.[26,29,53] The DMN has been associated with attentional processes in the brain including fluctuations in attentional control, or mind-wandering.[54] Mind wandering, defined as interruption of focused thought with task unrelated thought, is associated with and supported by the DMN.[55] The DMN is also the functional network associated with self-referential thinking. Self-referential thinking has been defined as examining external stimuli as strongly related to oneself or persona, such as evaluating the degree to which personality traits or certain words describe oneself.[56-58]

Interventions which aim at limiting mind wandering might lessen depressive rumination over time. Mindfulness itself is characterized by self-regulated present centered awareness.[59] It is the key component in clinically applied MBSR which may reduce mind wandering, as it brings the participant fully into the present moment.

A cross-sectional study investigated DMN activity in long term meditators versus those who were meditation naïve following a mindful meditation (MM) intervention, matching MBSR core tenants.[54] There was markedly reduced functional connectivity in

the PCC and mPFC seed regions in meditators versus controls ($p < 0.05$). Meditators also subjectively reported less mind wandering experiences, which was associated with lowered DMN activity. Mindfulness practices may specifically alter DMN activity and thus should be evaluated clinically as a potential nonpharmacological avenue of treatment for depression, as in this proposed study.[60]

2.5.3 Antidepressants and Default Mode Network Functional Connectivity

Recent studies utilizing antidepressants to treat MDD have evaluated treatment efficacy not only subjectively based on depressive symptom severity, but also changes in DMN activity. In a systemic review, 11 studies focused specifically on MDD and all showed baseline DMN hyperconnectivity, which is in line with a recent meta-analysis.[27,61] Within this review, an 8-week clinical trial assessed the effects of escitalopram on emotion processing and regulation within moderate-severe MDD.[62] A repeated-measure ANOVA confirmed that MDD patients had increased amygdala activation relative to HCs when anticipating negative stimuli. MDD individuals also showed heightened prefrontal activation when passively viewing negative pictures which was attenuated following antidepressant treatment, indicating that DMN FC is at least in part modifiable. However, the aforementioned conclusion cannot be considered a causal relationship because emotion regulation strategies were not assessed prior to this study.

Researchers studied the effect of a 12-week course of different antidepressants on DMN FC in depressed individuals.[63] Group ICA of imaging showed increased FC within the two subnetworks of the DMN of depressed individuals, consistent with prior studies.[35,64] Researchers also found that increased DMN dominance was associated with higher levels of maladaptive rumination and lower dominance with adaptive, reflective

rumination.[64] The mPFC hyperconnectivity persisted in recovered depressed individuals, possibly relating to the high rate of relapse in depression given this persistent activity despite antidepressant treatment with symptomatic improvement.

In a prospective, double blind, placebo-controlled trial, Posner and colleagues evaluated duloxetine's effect on DMN FC within individuals with dysthymic disorder (DD) compared to placebo control group.[65] Dysthymic disorder is differentiated from MDD through experience of less severe depression symptoms for at least 2 years. However, both disorders involve excessive rumination.[39] Individuals with DD had at baseline greater DMN connection density using the PCC as seed in whole brain resting state FC maps. Post hoc analysis within DD individuals showed that they had a statistically significant decrease in DMN connection density, so much so that it was at a level comparable to healthy controls, indicating normalization of DMN connectivity. Therefore, DMN FC could be used in future studies, such as this proposed RCT, as a neural correlate to monitor progression of depression.

In the aforementioned study, there was no statistically significant relationship found between normalization of DMN FC and reduction in depressive symptoms as measured by the Hamilton Depression Rating Scale, 24 Item (HAMD-24). There is a need for studies to further pursue this relationship between depressive symptoms and DMN activity rigorously and specifically to assess for possible correlation, which is what this proposed study hopes to contribute to.

2.6 Relevant Methodology

This section of the literature review below details a review of studies concerning relevant methodology used to validate our proposed study design, variables and outcome measures. A detailed explanation of proposed study methods can be found in Chapter 3.

2.6.1 Study Design and Setting

The proposed study will be a prospective, randomized controlled trial (RCT) primarily examining change in depression symptom severity in adult patients with mild-moderate MDD. Diagnosis will be based on self-rated and clinician rated questionnaires comparing three randomized groups. An experimental treatment group will participate in SKY, which is our primary exposure, along with continuation of their standard antidepressant regimen. A second adjunctive care group will use MBSR and their standard antidepressant treatment. Lastly, the standard care control group will continue antidepressant medications only. As a secondary aim, we will use resting state functional connectivity MRI (rsfcMRI) to determine changes in functional connectivity (FC) in the DMN both within and between the three participant groups.

RCTs are considered the gold standard for clinical research as the use of randomization eliminates potential bias inherent to other study designs. The prospective nature of this study enables researchers to analyze a causal relationship between interventions and outcomes. We chose not to use waitlist or placebo as our control condition in this study. It would be unethical to require MDD patients to stop antidepressants given the risk of discontinuation syndrome. Continuing a stable dose of antidepressants also reduces the risk of rebound phenomenon, where patients experience either higher rates of relapse or especially severe episodes of relapse following

discontinuation.[66] Therefore, our control group will continue their antidepressants at a stable dose without any adjunctive treatment.

Although antidepressant medications in combination with nonpharmacological therapy are recommended as first line for MDD, our study seeks to investigate whether additional interventions- SKY and MBSR- will be beneficial. We will take potential confounders into consideration, such as sex, age, and education level.[67-69] The equipoise principle of RCTs is fulfilled, as each group holds equal potential for depression severity reduction without superiority.[70] We seek to find effective and tolerable adjunctive treatments in addition to pharmacological therapy that promote improved rates of response and ultimate remission of depressive symptoms.

The study will recruit patients from the Yale University Undergraduate and Graduate campuses as well as specialty community outpatient clinics such as the Connecticut Mental Health Center and the Cornell Scott-Hill Health Center. These sites were chosen in order to reach a broader selection of participants with diverse socioeconomic, ethnic, and health care access backgrounds.

Participants will be recruited through flyer callouts, posted throughout Yale University Undergraduate and Graduate campuses to advertise to the university student population (See Appendix D). These recruitment flyers will also be posted at outpatient clinics to engage the community, specifically the Connecticut Mental Health Center, as well as the Cornell Scott-Hill Health Center. This does have the potential limitation of selection bias, as it includes mainly patients who are highly motivated and already connected to care at these clinics. However, this select group of patients are most able to

benefit from the proposed interventions as they require high compliance, and thus this limitation is acceptable.

2.6.2 Selection of Interventions

Given the high rate of recurrence of depressive symptoms despite adequate pharmacological treatment with or without psychotherapy, this study will focus on two adjunctive treatments to pharmacotherapy when treating MDD: Sudarshan Kriya Yoga (SKY) and Mindfulness Based Stress Reduction (MBSR).

2.6.2A Sudarshan Kriya Yoga

SKY was chosen as our primary intervention because it has been the most widely used breathwork in clinical studies and research.[1] SKY reliably consists of three different types of breathing: three stage Ujjayi or victory breathing, Bhastrika or bellows breathing, and Sudarshan Kriya or cyclical breathing. The four components of SKY- three stage slow ujjayi, bhastrika, “om” chanting, and Sudarshan Kriya- are performed with the eyes closed while sitting in a cross legged position, and breathing in and out through the nostrils (see Appendix A for SKY Breathwork Components).[4,71] Subjects within our proposed study will be taught the three components of SKY without yoga asanas or physical postures, om chanting, stretching, or meditation.[72] This will be done in order to isolate the antidepressant effects of breathwork specifically.

Within our literature review, there were deviations with the timing, frequency and duration of SKY as well as inconsistent incorporation of mindfulness, stress reduction tools, and yoga postures.[1-4,73] For example, one RCT solely focused on the three types of SKY breathing without any other mindfulness component over a duration of four weeks, with daily 30-minute sessions led by an Art of Living Foundation instructor for six days

per week.[1] Hamilton-West and colleagues (2019) incorporated SKY with mindfulness, stress relieving skills, and meditation.[2] The study period was four weeks, similar to Janakiramah's protocol (2000), but differed in frequency of sessions. A certified SKY instructor led four, one-hour sessions per week, with one weekend 2.5 hour workshop and four weekly 90 minute individual sessions for personalized feedback for all participants.

Another clinical trial taught SKY breathwork, om chanting, and mindfulness skills in addition to holding weekly self-help groups within a period of two weeks, but extended follow-up to six months.[3] There were ten, two-hour long instructor-led sessions for the initial two weeks, then weekly follow-up two hour sessions held for six months of follow-up. Participants were also expected to perform individual breathwork and mindfulness practices six days per week for an average duration of 20 minutes, which is similar to the randomized waitlist-controlled study performed by Sharma and colleagues.[4] In addition to private at-home practice, the study included yoga, mindfulness meditation, stress education and SKY breathwork for six 3.5-hour sessions during the first week of the study. Weeks 2 through 6 consisted of daily 1.5 hours of SKY training in addition to individual practice. Lastly, an open label study shortened the duration of SKY breathwork, self-reflection, meditation, yoga stretches, and stress coping strategies into an intensive 5-day period.[73] The first day consisted of 3 hours of instruction in the three main forms of breathwork, which was continued onto Day 2 alongside adjunctive strategies for 6.5 hours. The last few days consisted of a total of 10 hours of training, with home practice introduced on Day 5 for 20 minutes per day for 6 days per week. This assortment of SKY protocols illustrates a lack of standardization and thus a limiting factor in the existing literature.

The inconsistency in SKY protocol is a limiting factor in the literature with no superior format determined. For this reason, we chose to match the well tolerated and uniform MBSR protocol to our SKY protocol. This decision will allow for equivalence in exposure to both interventions, and highlight what MBSR lacks, which is a breathwork component.

2.6.2B Mindfulness Based Stress Reduction

MBSR was chosen as our mindfulness-based intervention (MBI) specifically because it has been the most widely studied MBI and has clinically proven high patient tolerability and compliance rates.[5,74] Originally used to treat chronic pain, MBSR has been applied to psychological and behavioral disorders with good effect.[75]

Typically, the course is set up as an 8-week program with one instructor-led 2.5 hour session per week. In each group session containing up to 30 people, participants are instructed on mindfulness meditation skills. While lying down with eyes closed during the body scan practice, participants focus attention on sensation from head to toe. This mindset is then maintained in sitting meditation.[6] Lastly, Hatha yoga consists of gentle body awareness brought about through physical movement and stretching. Outside of one weekly group meeting, individuals will complete a daily 45-minute mindfulness practice for six days per week. Audiotapes will be used early on but gradually tapered in use.

This standardized MBSR protocol described above was then applied to treatment of generalized anxiety and panic disorders fulfilling DSM-III criteria.[76] A repeated measures analysis of variance (ANOVA) showed highly significant reduction in anxiety and depression from pre to post treatment. The high rate of completion (92%) and

maintenance of practice in 90% of patients at 3-month follow-up was encouraging for future studies utilizing MBIs.

Baer and colleagues conducted a review of 22 studies using MBSR and MBCT for chronic pain and Axis-I disorders including depression relapse.[5] Post treatment effect sizes ranged from 0.15 to 1.65, with an overall independent mean effect size of 0.74 (SD= ± 0.39). Mean completion rate was 85% which demonstrated the high tolerability of MBIs. In future studies, adequate sample sizes will be needed to assure medium to large effect size. Furthermore, the studies rarely reported how they ensured treatment completion. Our study will incorporate a daily log sheet for patients to record their sessions, and individual instructor feedback will help bolster treatment integrity (See Appendix E for Daily Log Sheet).

Kabat-Zinn conducted the most extensive meta-analysis of MBSR program completion over a two-year period assessing 1,155 patients.[74] Researchers measured completion rate and found that 76% of patients completed the eight-week intervention in totality with a 15% drop out rate. This meta-analysis revealed MBSR to be an effective with high patient compliance within a variety of somatic and psychological disorders.

In this planned study, MBSR became the choice intervention for our mindfulness active control arm due to various studies demonstrating high rates of compliance, program completion and patient satisfaction. While a large portion of this study's MBSR protocol will parallel the original established by Kabat Zinn[75], our study will have one key differentiating factor: an online format. A meta-analysis analyzing the effectiveness of 15 RCTs using either websites or live virtual classrooms for MBIs in place of face-to-face MBIs showed improvements in depression with a small significant effect size.[13] A

pre-planned schedule with password protected links will be sent out to the MBSR as well as SKY group at the start of the study. Weekly live sessions will be scheduled in the evening hours to allow for participants' occupational or educational commitments to be met first. Given the prevalence of COVID-19, necessitating social distancing to reduce exposure and spread of the virus, this adjustment in MBSR protocol is both necessary and just.

The MBSR intervention will carry on for a period of eight weeks in total, matching the standard MBSR methodology. There will be one 2.5 hour session each week led by an instructor virtually with up to 30 people per group, who will teach three core mindfulness skills: full body scan, sitting meditation, and Hatha yoga. Individual individual practice is expected for 45 minutes per day, six days per week. Participants will have access to pre-recorded instructor guidance sent out via email. As is typical in MBSR programs, subjects will be encouraged to taper use of these audio recordings halfway through the intervention period. There is a one time, online 7.5 hour intensive workshop during the sixth week, with various days available for scheduling flexibility.

2.6.3 Primary Outcome Measures

The primary outcome measure of this proposed study is mean change in the 17-Item Hamilton Depression Rating Scale (HAM-D17) total score from baseline to post treatment at 8 weeks. A secondary questionnaire, the Beck Depression Inventory, Second Edition (BDI-II), will also be given at the same time points. The use of an objective, clinician rated score with a subjective, patient rated score will give greater legitimacy and validity to changes in depression severity due to this combined assessment of two perspectives.

The HAM-D17 is considered the gold standard in outcome measures within depression trials.[77] The following scores will be used to differentiate depression severity: no depression (0-7); mild depression (8-16); moderate depression (17-23); and severe depression (≥24).[78] Response will be defined as a reduction of ≥ 50% of HAM-D17 score obtained prior to treatment initiation, and remission will be a HAM-D17 score as ≤ 7.[79]

The BDI-II is a self-report questionnaire consisting of 21 items that is one of the most commonly used tools to evaluate depression symptom severity.[80] Importantly, all questions are based on DSM-IV diagnostic criteria for MDD and measured with a 4-point Likert scale.[81] This measure has also demonstrated good internal consistency (α= 0.91) and validated psychometric properties.[80] According to the BDI-II, the following scores will be used to delineate depression severity: minimal depression (0-13); mild depression (14-19); moderate depression (20-28); and severe depression (29-63).

2.6.4 Secondary Outcome Measure

The secondary outcome measure will be change in FC within the DMN, interpreted through seed-based analysis of resting state functional connectivity MRI (rsfcMRI). RsfcMRI evaluates functional connectivity within predefined brain regions by correlating low frequency blood oxygenation level dependent (BOLD) signal changes (<0.1 Hz) temporally. Scans will be performed at baseline prior to intervention and following completion. All subjects will undergo a 5-minute fMRI scan while resting quietly, given no specific instruction except to close their eyes and remain still, letting their minds wander freely. The time period and specific wording of instructions is most consistent with studies using rsfcMRI to evaluate the DMN.[35,54,63-65]

Brain activity can be measured through structural, effective or functional connectivity.[82] Functional connectivity is defined as temporal associations of synchronous neural activity between anatomically separate brain regions either at rest or during a task.[51,83] The DMN is notably most active at rest without any stimuli present.[26,23] Therefore, resting state functional connectivity MRI (rsfcMRI) will be used rather than task-based fMRI.[84]

Seed based analysis serves as a widely used method with easy interpretability for measuring FC. The average measurement of the time series within a seed region is linearly correlated with all other voxels, creating a seed-based functional connectivity map.[85] A drawback when using seed-based analysis rather than independent component analysis (ICA) or graph theory is that areas of interest are restricted to predefined brain regions only. In our proposed study, this definition dependence is a strength as we are interested in a seed region integral to the DMN: the posterior cingulate cortex (PCC).

The PCC is the most reliable region shown to reveal FC within the DMN.[51,86] In our study, we will use an *a priori* seed voxel within the PCC (x= −8, y= −56, z= 26) based on the Montreal Neurological Institute coordinates. This specific area was decided upon after an extensive review of prior fMRI studies also focusing on the DMN within a mood disorder patient population. Additionally, it is anatomically similar to the seed regions that other researchers have used to define the DMN.[26,31,41,51,54,65,87,88]

All fMRI scans will be obtained at baseline and post intervention at the conclusion of Week 8 on the same Siemens 3-Tesla whole body scanner at the Yale Magnetic Resonance Research Center. Patients will be instructed to lie in the scanner awake without stimuli and not think of anything in particular while their eyes are

closed.[83] A Velcro strap placed over the forehead will reduce head motion artifact. Cardiac and respiratory physiologic noise will be monitored through a photoplethysmography on a finger of the left hand and a pneumatic belt positioned at the level of the upper abdomen.

Functional MRI data will be obtained through a T*2 weighted gradient-recalled echo spiral pulse sequence with the following standardized parameters: repetition time/ echo time= 2000 msec/30 msec, flip angle= 80°, 1 interleave, field of view= 200 x 200 mm^2, matrix= 64 x 64, slices= 28.[35] These parameters were chosen because they mirror the same 5-minute interval of our resting state fMRI scan. We chose to use T*2 imaging rather than T*1 imaging because there is higher temporal resolution and greater sensitivity to blood flow and oxygenation in T*2 imaging.[85]

Following imaging, physiologic noise will be removed through pre-processing prior to analysis. Measures of FC are highly dependent on the quality of BOLD signal. The signal can become distorted through artifact, such as cardiac and respiratory cycle noise.[89,90] A type I error can occur if the noise components correlate with enough strength to reach threshold, yet there is no neuronal correlation. Conversely, a type II error can occur when there is actual temporal synchronization between the seed ROI and other voxels which is not found due to overlying physiologic noise.[91] Pre-processing will consist of standard steps including slice-timing correction, motion correction, normalization, spatial smoothing, and linear trend removal.

2.6.5 Confounders

Sex, age and education are potential confounders which threaten internal validity, and therefore must be taken into account in order to avoid type I error.[92]

Female predominance within depression studies reflects the core concept of gender difference in depression.[93] One meta-analysis found a 1.95 odds ratio for gender differences in diagnosis of MDD. Furthermore, a proportion of studies and clinical trials in our current literature review also demonstrated a predominance of women within depressed populations.[2-5,13,14,94] Within the same review, age was the strongest predictor of effect size, with a peak of effect size in adolescence that stabilized in adulthood.

Initially, our RCT study design will reduce potential confounding effects via randomization and creating groups that are adequately comparable in terms of potentially confounding variables and size. In addition, analysis of covariance (ANCOVA) will be applied to increase statistical power after data collection.

2.7 Conclusion

This current literature review demonstrates the unique application and potential effectiveness of both SKY and MBSR as adjunctive antidepressant therapies, measured through symptomatic relief and change in DMN FC through rsfcMRI. Depression affects all age groups and is highly prevalent condition within the COVID-19 pandemic. We have outlined areas for improvement within the current studies available concerning the variables of this study, which our proposed study will address. Analysis of these studies illustrated the components of our study design and the necessity of this study as we seek to offer and expand current options for treatment of depression. Ultimately, this study will add to the current literature focusing on non-pharmacological adjuvant treatment options for mild to moderate depression.

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CHAPTER 3: STUDY METHODS

3.1 Study Design

We will conduct a prospective, randomized controlled trial (RCT) to determine if there is a change in depression symptom severity and, secondarily, change in functional connectivity in the Default Mode Network (DMN). The sample consists of adults with mild to moderate major depressive disorder (MDD) aged 18 – 65 years old who are randomized into one of three groups. The experimental treatment group will participate in Sudarshan Kriya Yoga (SKY) as their adjunctive therapy in addition to their current pharmacological regimen. An adjunctive care group will receive the established and standardized Mindfulness Based Stress Reduction (MBSR) therapy in addition to their current pharmacological regimen. A standard care group will continue to receive their current pharmacological therapy. The goal is to examine change in symptoms of depression within and between the three groups to investigate feasibility and efficacy of adjunctive nonpharmacological treatments. Potential confounders, including sex, age, and education, will be adjusted for in the study design and analysis.

3.2 Study Population and Sampling

The source population in this study is adults aged 18-65 years old with mild to moderate depression, as defined by the diagnostic criteria as set forth by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). From the pool of subjects who respond to study recruitment efforts through an intake form, we will utilize

convenience sampling based on meeting all inclusion criteria and no exclusion criteria until an adequate sample size is reached during rolling enrollment. Once an adequate sample size is reached, researchers will use online software to block randomize subjects into each of the three study groups in order to have equal group size. (See Appendix F for Intake Form).

3.2.1 Inclusion Criteria

Subjects will be adult outpatients aged 18-65 years old. All participants will be assessed by a psychiatrist or clinical psychologist to meet criteria for mild-moderate major depression (MDD), as the goal of the study is to investigate adjunctive, nonpharmacological therapy in patients who continue to have symptoms of depression in the mild-moderate range despite their current pharmacological regimen. The criteria for inclusion are:

1) Current diagnosis of MDD for at least 2 years.

2) Fulfillment of criteria according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID for DSM-IV) for a single or recurrent major depressive episode.

3) Have current self-reported mild-moderate depression symptoms within a total score range of 8-23 for the 17-item Hamilton Depression Rating Scale (HAM-D17) and a range of 14-28 for the Beck Depression Inventory, Second Edition (BDI-II).

4) All participants will need to be on a stable (≥ 8 weeks) dose of antidepressant(s). If a pharmacological regimen is changed, participants can continue in the study but may be removed from study analysis as appropriate.

5) Must be right-handed.

6) Must have access to a personal smart phone, computer, or tablet to access remote online sessions.

3.2.2 Exclusion Criteria

The exclusion criteria for the selected study population includes any comorbid Axis I disorders, bipolar disorder, psychosis, alcohol or substance abuse within the past 6 months, contraindications to MRI (e.g., metallic implants, pacemakers, or claustrophobia), active suicidality, seizure disorder, history of head injury that resulted in loss of consciousness, neurological disorder, brain degenerative disease, history of electroconvulsive therapy, history of transcranial magnetic stimulation, history of stroke or significant head injury, and current yoga, meditation or breathwork practices.

3.3 Recruitment

Participants will be recruited through IRB approved flyer callouts posted throughout Yale University Undergraduate and Graduate campuses to advertise to the university student population. Bulletin board advertisements will also be posted at specialty outpatient clinics, including the Connecticut Mental Health Center and Cornell Scott-Hill Health Center, to advertise to a more diverse clinical population and to offer nonpharmacological, remote treatment options to the greater New Haven community. See Appendix D for sample recruitment flyer.

3.4 Subject Protection and Confidentiality

This will be an Institutional Review Board (IRB)-approved, Health Insurance Portability and Accountability Act (HIPAA)-compliant prospective randomized

controlled trial. This study will obtain informed, written consent from each participant that explicitly describes the group treatment sessions (See Appendix G). Participants will be informed that during live remote video sessions for both MBSR and SKY, an instructor will be teaching a group of less than 30 individuals. No sessions will ever be recorded, and a password protected link will be sent out for each session. Participants have the option of keeping their videos on in order to receive feedback. All members of the research team will complete the Human Subjects Protection Training and HIPAA Privacy training. No members will have external financial or non-financial interests related to the research which may affect the protection of individuals volunteering for research. Patient information will be protected through exclusive access on secure, password encrypted institutional servers. Each participant will be given an ID code to protect privacy. Participants will know explicitly what information will be used for research purposes and be informed of our confidentiality and privacy practices.

Given that this study will be advertised within the undergraduate and graduate Yale University campus grounds, all requirements will be fulfilled in accordance with Yale IRB Policy 350 *Participation of Yale Students, Fellows, Trainees, or Employees in Research*. Additionally, we will fulfill requirements when obtaining clear, informed consent as set by the Yale IRB Policy 200 *Informed Consent for Human Research.* The consent form will fully explain the purpose of this study and anticipated study duration, emphasizing the group format of the study, identifying pertinent procedures with ensuing comprehensive descriptions, and detailing the subject risk and benefits. The participants will be made aware that participation is completely voluntary and that they can withdraw at any point during the study without consequence. Contact information will be provided

should subjects have any questions, comments or concerns. Final submission of the necessary IRB forms will be made using the IRES IRB system.

3.5 Study Variables and Outcome Measures

3.5.1 Independent Variables

The independent variables in this study are SKY and MBSR as adjunctive therapies to standard, stable dose antidepressant treatment for MDD. The mindfulness intervention, MBSR, will be based on the original protocol developed by Kabat-Zinn, with relatively minimal changes to adapt to an online context.[1] Meditation sessions will be led by a certified MBSR teacher conducted through live remote video. The intervention duration will be for 8 weeks, weekly 2.5 hours group with less than 30 people per group. These sessions will be complemented with an independent at-home practice approximately 45 minutes per day for 6 days per week, as well as a day-long online mindfulness retreat on the sixth week of the intervention (9am-4pm). The SKY protocol will mirror the MBSR administration. It will also be taught via live remote video sessions, where once again participants have the option of turning their videos or microphones on if desired in order to receive feedback from the instructor. A trained SKY instructor from the Art of Living Foundation will lead participants through the main SKY breathing techniques once per week for 2.5 hours, which is structurally equivalent to the MBSR protocol. Participants will perform breathwork independently 45 minutes per day for 6 days per week, and also participate in an online day long retreat during the sixth week consisting of intensive breathwork and individual feedback (9am-4pm). The

specific elements of both MBSR and SKY interventions have been described previously in detail (see Chapter 2).

3.5.2 Primary Dependent Variable

The primary dependent variable is change in severity of depression symptoms, as measured by the clinician-rated 17-Item Hamilton Depression Rating Scale (HAM-D17) which controls for observation bias, and secondarily by the self-rated Beck Depression Inventory, Second Edition (BDI-II). The questionnaires are completed at baseline (Week 0) and again at the end of the study (Week 8). The HAM-D17 will utilize the following scoring: severe depression (≥24), moderate depression (17-23), mild depression (8-16), and no depression (0-7).[2] The BDI-II consists of 21 questions which are self-completed and consistent with the DSM-IV criteria used to both diagnose and treat depression. The following established scoring will be used: severe depression 29–63, moderate depression 20–28, mild depression 14–19, and minimal depression 0–13.[3]

3.5.3 Secondary Dependent Variable

The second aim of this study is to examine how the two adjuvant treatments- SKY and MBSR- effect functional connectivity (FC) within the DMN, in comparison to isolated standard pharmacological therapy. Therefore, the secondary outcome of interest in this study will be change in FC of the DMN within each group as well as across all three groups. Participants will undergo a 5-minute resting state functional connectivity MRI (rsfcMRI) scan performed at Week 0 (baseline) and post assessment at the end of Week 8 to assess for change over time on the same Siemens 3-Tesla whole-body MRI scanner. Changes in functional connectivity within the DMN will be assessed using an *a*

priori defined posterior cingulate cortex (PCC) (x=-8, y=-56, z=26) as primary seed region of interest (ROI) for seed-based functional connectivity analysis.

3.5.4 Potential Confounding Variables

Possible confounding variables within this study include sex, age and education level. An advantage of the block randomization RCT design is to minimize the effects of possible confounding variables. However, as this cannot be guaranteed and confounders may influence the results of the study, an analysis of covariance (ANCOVA) statistical approach will be utilized to account for potential effects of these confounders.[4]

3.6 Methodology Considerations

3.6.1 Blinding

It is not possible to double-blind this proposed study, as explicit patient participation in SKY and MSBR is required. However, there are other opportunities to incorporate blinding methods into the study design and elements. For example, SKY and MBSR instructors will only be exposed to people who are in their respective groups. These teachers will not know the randomized data number assigned to each participant nor will they be involved in data analysis. In addition, the clinician who is rating the HAM-D17 questionnaire at the beginning and conclusion of the study will not know which group the subject was randomized to and will not be involved in treatment administration. Patients will also be informed to not tell the outcome assessor which treatment they received.

3.6.2 Assignment of Intervention

Following meeting the inclusion and none of the exclusion criteria, eligible participants will be randomly assigned to either intervention group or continue their stable antidepressant regimen. Block randomization will then be carried out to allow for an equal number of subjects per group. The randomization software will be completed by a computer specialist external to the study.

3.7 Data Collection

Methods for data collection include questionnaires, such as the HAM-D17 and BDI-II, and neuroimaging data acquired from rsfcMRI scans. Initially, participants will fill out an intake form that will obtain name, age, sex, race/ethnicity, birth date, highest level of education achieved, and the type, frequency, and duration of antidepressant medications that are being taken. Other considerations, including exclusion criteria, will also be assessed through this intake form. All participants will undergo a standardized psychiatric evaluation using the SCID for DSM-IV. They will complete the clinician rated HAM-D17 as well as the self-administered BDI-II in order to get a convergence of object and subjective perspectives. All subjects will also undergo rsfcMRI scans at the baseline and conclusion of the study. These scans will be performed on the same Siemens 3-Tesla MRI scanner at the Yale Magnetic Resonance Research Center, which is in close proximity to the academic campuses, medical centers, and community from which our participants will be recruited from. Lastly, participant compliance with home practice will be assessed based on self-completed participant log sheet records that will be collected at the end of the study.

3.8 Sample Size Calculation

The calculation for our sample size was performed using the G*Power version 3.1 with ANCOVA to compare change in pre-intervention and post-intervention HAM-D17 total scores given the confounders of sex, age, and education level. The reviewed literature is typically powered based on the primary outcome measure to a significance level of 5% and power of 80%, which our study will follow. We utilized a medium effect size, consistent with the studies reviewed also using similar outcome measures.[5-7] Our sample size was initially calculated to be 196 participants. We do anticipate a 10% drop out rate, which led to a sample size of 213 participants. Reasons for drop out will be recorded and tracked to identify any patterns of drop out that could potentially impact results.[8] Our complete sample size calculation can be found in Appendix H.

3.9 Statistical Analysis

Intention to treat (ITT) analysis will be used to analyze results in this prospective RCT. Initially, baseline demographic characteristics that are continuous or dichotomous in nature, including sex, age, and education levels of all enrolled participants, will be analyzed using a chi-squared test. A correlation matrix will illustrate the cross correlations between demographic variables and depression ratings.

3.9.1 Primary Outcome

Mean total HAM-D17 and BDI-II scores with standard deviation will be obtained from each of the three groups both pre and post intervention. Paired *t-tests* will be used to assess significant difference in depression symptom severity within each group based on

mean difference in total HAM-D17 scores as primary outcome, and each *t-test* will be two-sided with a significance of $p< 0.05$. In order to assess significant change in depression symptom severity based on HAM-D17 between the three groups post-intervention, ANCOVA will be performed with group as between subject factor and baseline subject characteristics of sex, age and education level as covariates. The same procedure will be repeated for the BDI-II questionnaire mean total scores.

3.9.2 Secondary Outcome

Functional connectivity changes within the DMN using the posterior cingulate cortex (PCC) as the seed region of interest (ROI) (x=-8, y=-56, z=26) will be analyzed through seed-based analysis both within and between each of the three groups at baseline (Week 0) and the conclusion of the study at the end of Week 8. We will obtain average time series from within the seed region and use the Pearson correlation coefficient to capture linear, temporally dependent BOLD signal changes that indirectly reflect synchronized activity between the PCC and other brain regions.[9] We will then z-transform all functional connectivities with a Fisher's r-to-z transformation for normal distribution. The resultant connectivity map will show all voxels that had a significant time dependent neural activity correlation with the PCC and thus reflect the strength of functional connectivity, with a false discovery rate of 0.05 ($p_{FDR} <0.05$).[10,11]

Within group analysis will next be done by entering z-scores into a series of one-sample *t-tests* in SPM 12, comparing baseline and post-intervention scans with a significance threshold of $p< 0.05$ (FDR corrected) for each group. This will determine cortical regions with statistically significant association with the PCC seed ROI within each of the three groups of participants after treatment completion.

Secondly, between group analysis of FC will be accomplished using ANCOVA with group as between subject factor and sex, age and education level as covariates ($p<0.05$, FDR corrected, minimum 21 voxels in a cluster). ANCOVA has the lowest variance, highest power, and nominal 95% CI coverage relative to ANOVA-POST and ANOVA-CHANGE, making it the preferred analytical tool.[4]

3.9.3 Image Pre-Processing

Images will be pre-processed using the Statistical Parametric Mapping Software, Version 12 (SPM 12), including slice-timing correction using sinc interpolation, 3D motion correction using sinc interpolation, normalization into the Montreal Neurological Institute space, and spatial smoothing with a 3D Gaussian kernel (full-width-at-half-maximum of 4 mm).[10,12] These measures will suppress high frequency signals that reflect spatial noise as well as enhance low frequency signals within the .01 Hz to .08 Hz range, and lastly result in linear trend removal. Subjects who have excessive head motion (>2.5mm translation or > 5° rotation) will be excluded from future analysis.[12] The first five images will be discarded to allow for magnetic equilibrium and discard magnetic saturation.

Physiological noise from cardiorespiratory components will be monitored through a photoplethysmography placed on the finger of the left hand and a pneumatic belt positioned at the level of the upper abdomen. Cardiac and respiratory artifact will be removed using the RETROICOR algorithm and by removing low-frequency respiratory rate and heart rate effects.[13,14]

3.10 Timeline and Resources

Pending IRB approval, the study will be completed within 2 years, encompassing patient recruitment and protocol completion. After interested participants contact the research team through an email which will be listed on all IRB approved flyers, an online screening will be done to determine eligibility. Screen consists of an intake survey detailing their name, age, gender, level of education, psychological disorders, frequency and dosage of any antidepressant medications, and exclusion criteria (See Appendix F for Intake Form). A clinical psychologist or psychiatrist will administer the SCID for DSM-IV and the patient will complete the BDI-II. We will use a rolling enrollment period of 12 months or until the calculated sample size of 213 is reached. Following signature of an informed consent form upon enrollment, participants will be block randomized into one of three groups: pharmacological therapy with SKY, pharmacological therapy with MBSR, or continuing standard pharmacological therapy without adjunctive therapy (serving as control). All adults will be educated on the use of password protected links for either MBSR or SKY, as well as given flexible time slots to obtain baseline fMRI imaging. Data analysis will be completed within 2-3 months following completion.

Personnel to be included in this study include a principal investigator, a co-principal investigator, clinical psychologist or psychiatrist to rate baseline and post intervention HAM-D17 questionnaires, a computer specialist to randomize eligible subjects, Yale Magnetic Resonance Research center lab assistant to run rsfcMRI scans, fMRI imaging analyst, a certified SKY instructor, and a certified MBSR instructor. There will also be one physician associate student to aid in recruitment, data analysis, and statistical analysis.

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CHAPTER 4: CONCLUSION

4.1 Advantages

When reflecting on our study's advantages, the prospective, randomized controlled trial (RCT) design reduces bias through randomization. The most relevant strength of the experimental intervention of this study- Sudarshan Kriya Yoga (SKY)- lies in the fact that breathwork is both an economically sound and socially just practice. SKY could be used to stabilize a patient's current treatment, decreasing the number of prescriptions which enable financial savings.[1,2]

This practice can be used on a multitude of patients, including those with physical disability. It is easy to administer across urban, suburban, and rural regions given the online format of the intervention. Once the basic cadence of breathwork is memorized, then the patient can proceed at leisure in terms of deciding when to practice, with no need to travel anywhere, take time off work, or find childcare.

The study design will establish a potential standardized SKY protocol, as the current literature reviewed by researchers was inconsistent. Furthermore, matching the SKY protocol to the well-established and tolerated Mindfulness Based Stress Reduction (MBSR) protocol will allow for equivalence in the exposure to the interventions in our study. The design is also feasible for future studies due to its online format. No in-person MBSR or SKY sessions will be required, allowing participants to complete their assigned intervention in the comfort of their own homes. In addition, focusing specifically on depression during the COVID-19 pandemic is especially pertinent given rising isolation and prevalence of depression.[3] Increased prevalence of depression may persist while

COVID-19 health and safety policies remain, which highlights the relevance of an at home, easy to use, individual practice like SKY.

4.2 Disadvantages

Although this study contains significant advantages in terms of study design and contribution to the current literature, there are some limitations. Convenience sampling is nonrandomized, resulting in potential selection bias and lower external validity. Furthermore, the target patient population was specified to those mild-moderate depression already on antidepressant medications within the Yale Health System and greater Connecticut areas. This study was designed to exclude severely depressed patients because they are often refractory to typical treatment and require escalation to high intensity therapies.[4] Our study may have lower external validity, as the patient population is not completely representative of the entire population of depressed individuals. However, if this intervention is found to be successful in the selected mild-moderate population, we would think carefully about how this intervention could be assessed safely in a population with severe depression, such as in an inpatient setting.

The study protocol will control for physiologic noise during rsfcMRI scans through a photoplethysmography and pneumatic belt. However, it does not control for participant related factors that could have affected BOLD signal. The vasoconstrictive effect of caffeine affects cerebral blood flow which in turn alters BOLD signal.[5] Aside from caffeine, intake of food, nicotine, and alcohol before a resting state fMRI scan can have significant effects on BOLD signal. Given that MRI times will be scheduled throughout the day, the researchers did not want to be overly restrictive to a vulnerable population.

Lastly, treatment adherence is a common threat to MBI effectiveness.[6,7]. Non-adherence occurs when participants do not complete the intervention in entirety with the minimum frequency as defined in study protocol. Regular practice is essential to obtain ultimate benefit.[8] Although the study participants will complete a self-reported daily log, it might be more accurate to have researcher personnel observed SKY or MBSR sessions to ensure completeness and accuracy. Future studies without the current social distancing requirements and COVID-19 health and safety conditions could implement therapists to observe or lead individual practice sessions.

4.3 Clinical Significance

This study is clinically significant because it examines the effectiveness of an adjunctive treatment for MDD and can broaden our understanding of the underlying mechanisms amongst breath-oriented therapy, depression, and functional connectivity within the brain. If this study demonstrates effectiveness and high patient tolerability with SKY, breathwork could become more widely accessible for patients, especially those undergoing financial hardship and already at risk for health disparities. Instead of increasing dosage of antidepressants, SKY could be added as a low risk, low cost adjunctive treatment to work in conjunction with the medications. In conclusion, improving availability of treatment options and programs for individuals with mild to moderate depression can reduce escalation of treatment, reduce relapse rates, and result in greater rates of remission.[9] This study has the potential to improve treatment options for those with MDD through a cost effective and individually empowering additional remedy: breathwork.

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Appendix A: Sudarshan Kriya Yoga Breathwork Components

Practice	**Breath Rate (cycles/min, cpm)[a]**	**Duration (minutes)[b]**
3-stage victory breathing	2-4 cpm	7 minutes
Bellows breathing/ Bhastrika	30-40 cpm	3 minutes
Sudarshan Kriya cyclical breathing	8-180 cpm	10 minutes
Rest Period	N/A	5 minutes

[a] Approximate range

[b] Practice duration includes rest periods

Appendix B: 17 Item Hamilton Depression Rating Scale (HAM-D 17)

Hamilton Depression Rating Scale (HDRS)

Reference: **Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62**

Rating Clinician-rated

Administration time 20–30 minutes

Main purpose To assess severity of, and change in, depressive symptoms

Population Adults

Commentary

The HDRS (also known as the Ham-D) is the most widely used clinician-administered depression assessment scale. The original version contains 17 items ($HDRS_{17}$) pertaining to symptoms of depression experienced over the past week. Although the scale was designed for completion after an unstructured clinical interview, there are now semi-structured interview guides available. The HDRS was originally developed for hospital inpatients, thus the emphasis on melancholic and physical symptoms of depression. A later 21-item version ($HDRS_{21}$) included 4 items intended to subtype the depression, but which are sometimes, incorrectly, used to rate severity. A limitation of the HDRS is that atypical symptoms of depression (e.g., hypersomnia, hyperphagia) are not assessed (see SIGH-SAD, page 55).

Scoring

Method for scoring varies by version. For the $HDRS_{17}$, a score of 0–7 is generally accepted to be within the normal range (or in clinical remission), while a score of 20 or higher (indicating at least moderate severity) is usually required for entry into a clinical trial.

Versions

The scale has been translated into a number of languages including French, German, Italian, Thai, and Turkish. As well, there is an Interactive Voice Response version (IVR), a Seasonal Affective Disorder version (SIGH-SAD, see page 55), and a Structured Interview Version (HDS-SIV). Numerous versions with varying lengths include the HDRS17, HDRS21, HDRS29, HDRS8, HDRS6, HDRS24, and HDRS7 (see page 30).

Additional references

Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967; 6(4):278–96.

Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry 1988; 45(8):742–7.

Address for correspondence

The HDRS is in the public domain.

Hamilton Depression Rating Scale (HDRS)

PLEASE COMPLETE THE SCALE BASED ON A STRUCTURED INTERVIEW

Instructions: for each item select the one "cue" which best characterizes the patient. Be sure to record the answers in the appropriate spaces (positions 0 through 4).

1 DEPRESSED MOOD *(sadness, hopeless, helpless, worthless)*
- 0 |__| Absent.
- 1 |__| These feeling states indicated only on questioning.
- 2 |__| These feeling states spontaneously reported verbally.
- 3 |__| Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.
- 4 |__| Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2 FEELINGS OF GUILT
- 0 |__| Absent.
- 1 |__| Self reproach, feels he/she has let people down.
- 2 |__| Ideas of guilt or rumination over past errors or sinful deeds.
- 3 |__| Present illness is a punishment. Delusions of guilt.
- 4 |__| Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

3 SUICIDE

0 |__| Absent.
1 |__| Feels life is not worth living.
2 |__| Wishes he/she were dead or any thoughts of possible death to self.
3 |__| Ideas or gestures of suicide.
4 |__| Attempts at suicide (any serious attempt rate 4).

4 INSOMNIA: EARLY IN THE NIGHT

0 |__| No difficulty falling asleep.
1 |__| Complains of occasional difficulty falling asleep, i.e. more than ½ hour.
2 |__| Complains of nightly difficulty falling asleep.

5 INSOMNIA: MIDDLE OF THE NIGHT

0 |__| No difficulty.
1 |__| Patient complains of being restless and disturbed during the night.
2 |__| Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).

6 INSOMNIA: EARLY HOURS OF THE MORNING

0 |__| No difficulty.
1 |__| Waking in early hours of the morning but goes back to sleep.
2 |__| Unable to fall asleep again if he/she gets out of bed.

7 WORK AND ACTIVITIES

0 |__| No difficulty.
1 |__| Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.
2 |__| Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).
3 |__| Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
4 |__| Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

8 RETARDATION (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)

0 |__| Normal speech and thought.
1 |__| Slight retardation during the interview.
2 |__| Obvious retardation during the interview.
3 |__| Interview difficult.
4 |__| Complete stupor.

9 AGITATION

0 |__| None.
1 |__| Fidgetiness.
2 |__| Playing with hands, hair, etc.
3 |__| Moving about, can't sit still.
4 |__| Hand wringing, nail biting, hair-pulling, biting of lips.

10 ANXIETY PSYCHIC

0 |__| No difficulty.
1 |__| Subjective tension and irritability.
2 |__| Worrying about minor matters.
3 |__| Apprehensive attitude apparent in face or speech.
4 |__| Fears expressed without questioning.

11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as:

gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching
cardio-vascular – palpitations, headaches
respiratory – hyperventilation, sighing
urinary frequency
sweating

0 |__| Absent.
1 |__| Mild.
2 |__| Moderate.
3 |__| Severe.
4 |__| Incapacitating.

12 SOMATIC SYMPTOMS GASTRO-INTESTINAL

0 |__| None.
1 |__| Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
2 |__| Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

13 GENERAL SOMATIC SYMPTOMS

0 |__| None.
1 |__| Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
2 |__| Any clear-cut symptom rates 2.

14 GENITAL SYMPTOMS (symptoms such as loss of libido, menstrual disturbances)

0 |__| Absent.
1 |__| Mild.
2 |__| Severe.

15 HYPOCHONDRIASIS

0 |__| Not present.
1 |__| Self-absorption (bodily).
2 |__| Preoccupation with health.
3 |__| Frequent complaints, requests for help, etc.
4 |__| Hypochondriacal delusions.

16 LOSS OF WEIGHT ***(RATE EITHER a OR b)***

a) According to the patient:	**b) According to weekly measurements:**
0 |__| No weight loss.	0 |__| Less than 1 lb weight loss in week.
1 |__| Probable weight loss associated with present illness.	1 |__| Greater than 1 lb weight loss in week.
2 |__| Definite (according to patient) weight loss.	2 |__| Greater than 2 lb weight loss in week.
3 |__| Not assessed.	3 |__| Not assessed.

17 INSIGHT

0 |__| Acknowledges being depressed and ill.
1 |__| Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 |__| Denies being ill at all.

Total score: |__|__|

Appendix C: Beck Depression Inventory, Second Edition (BDI-II)

BDI - II

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully. And then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
   0. I do not feel sad.
   1. I feel sad much of the time.
   2. I am sad all the time.
   3. I am so sad or unhappy that I can't stand it.

2. Pessimism
   0. I am not discouraged about my future.
   1. I feel more discouraged about my future than I used to.
   2. I do not expect things to work out for me.
   3. I feel my future is hopeless and will only get worse.

3. Past Failure
   0. I do not feel like a failure.
   1. I have failed more than I should have.
   2. As I look back, I see a lot of failures.
   3. I feel I am a total failure as a person.

4. Loss of Pleasure
   0. I get as much pleasure as I ever did from the things I enjoy.
   1. I don't enjoy things as much as I used to.
   2. I get very little pleasure from the things I used to enjoy.
   3. I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
   0. I don't feel particularly guilty.
   1. I feel guilty over many things I have done or should have done.
   2. I feel quite guilty most of the time.
   3. I feel guilty all of the time.

6. Punishment Feelings
   0. I don't feel I am being punished.
   1. I feel I may be punished.
   2. I expect to be punished.
   3. I feel I am being punished.

7. Self-Dislike
   0. I feel the same about myself as ever.
   1. I have lost confidence in myself.
   2. I am disappointed in myself.
   3. I dislike myself.

8. Self-Criticalness
   0. I don't criticize or blame myself more than usual.
   1. I am more critical of myself than I used to be.
   2. I criticize myself for all of my faults.
   3. I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
   0. I don't have any thoughts of killing myself.
   1. I have thoughts of killing myself, but I would not carry them out.
   2. I would like to kill myself.
   3. I would kill myself if I had the chance.

10. Crying
   0. I don't cry anymore than I used to.
   1. I cry more than I used to.
   2. I cry over every little thing.
   3. I feel like crying, but I can't.

11. Agitation
   0. I am no more restless or wound up than usual.
   1. I feel more restless or wound up than usual.
   2. I am so restless or agitated, it's hard to stay still.
   3. I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest
   0. I have not lost interest in other people or activities.
   1. I am less interested in other people or things than before.
   2. I have lost most of my interest in other people or things.
   3. It's hard to get interested in anything.

13. Indecisiveness
   0. I make decisions about as well as ever.
   1. I find it more difficult to make decisions than usual.
   2. I have much greater difficulty in making decisions than I used to.
   3. I have trouble making any decisions.

14. Worthlessness
   0. I do not feel I am worthless.
   1. I don't consider myself as worthwhile and useful as I used to.
   2. I feel more worthless as compared to others.
   3. I feel utterly worthless.

15. Loss of Energy
   0. I have as much energy as ever.
   1. I have less energy than I used to have.
   2. I don't have enough energy to do very much.
   3. I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0. I have not experienced any change in my sleeping.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0. I am not more irritable than usual.
1. I am more irritable than usual.
2. I am much more irritable than usual.
3. I am irritable all the time.

18. Changes in Appetite

0. I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0. I can concentrate as well as ever.
1. I can't concentrate as well as usual.
2. It's hard to keep my mind on anything for very long.
3. I find I can't concentrate on anything.

20. Tiredness or Fatigue

0. I am no more tired or fatigued than usual.
1. I get more tired or fatigued more easily than usual.
2. I am too tired or fatigued to do a lot of the things I used to do.
3. I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0. I have not noticed any recent change in my interest in sex.
1. I am less interested in sex than I used to be.
2. I am much less interested in sex now.
3. I have lost interest in sex completely.

Total Score: _____

Appendix D: Recruitment Flyer

Volunteers Needed for Participation in Research Study

We are investigating the incorporation of Sudarshan Kriya Yoga breathwork as well as Mindfulness Based Stress Reduction in addition to antidepressants for treatment of mild to moderate major depressive disorder.

Who can participate?

Adults aged 18-65 years old with a diagnosis of mild to moderate depression currently on antidepressant medications.

What will be asked of you?

You will be asked to participate in an online, certified instructor led, randomized additional treatment option- either Sudarshan Kriya Yoga breathwork or Mindfulness Based Stress Reduction- or continue your current antidepressant medication for a period of 8 weeks with daily practice sessions required. You will undergo an fMRI scan both before and after the intervention, as well as participate in 2 surveys to determine change in depression severity following completion of the study.

If you are interested in participating or have any questions, please do not hesitate to contact us at: 203-XXX-XXXX or researchteam@yale.edu

Appendix E: Daily Log Sheet

Week	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Week 1						
Week 2						
Week 3						
Week 4						
Week 5						
Week 6						
Week 7						
Week 8						

Appendix F: Intake Form

Name: _____
Participant ID code: _____
Date: __/__/____
Age: ___

Gender: Male Female
Education:

- No high school diploma
- High school diploma
- Associate's degree or 2 years of college
- Bachelor's degree
- Master's degree
- PhD or professional degree

When were you diagnosed with major depressive disorder?

- < 2 years ago
- > 2 years ago

Duration of current depressive episode

- < 1 week
- 1-2 weeks
- 2-3 weeks
- 3-4 weeks
- 1 month
- 2 months
- 3 months
- 4 months
- 5 months
- 6 months

Current antidepressant medications, dosages and duration:

_____
_____
_____
_____

Are you right-handed? Yes No
Do you have access to a personal smart phone, computer, or tablet? Yes No
Are you currently being treated for any other mood disorder? Yes No
- If "yes", please write down which other disorder: _____

Do you have Bipolar disorder? Yes No
Have you ever experienced psychosis? Yes No
Any excessive alcohol or substance use within the past 6 months? Yes No
Do you have any metallic implants or a pacemaker? Yes No
Are you claustrophobic? Yes No
Are you currently being managed for active suicidal thoughts? Yes No
Do you have a seizure disorder? Yes No

Any history of head injury or trauma that resulted in a loss of consciousness?
Yes No
Do you have any neurological disorders? Yes No
Do you have a brain degenerative disease? Yes No
Have you undergone electroconvulsive therapy before or transcranial magnetic stimulation? Yes No
Any history of stroke or significant head injury? Yes No
Do you maintain a current yoga, breathwork, or meditative practice? Yes No

---

TO BE COMPLETED BY RESEARCHER:
HAM-D 17 total score, baseline: _____
BDI-II total score, baseline: _____

Appendix G: Written Consent Form

WRITTEN CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

Study Title: Sudarshan Kriya Yoga and Alteration in Depression Severity and Default Mode Network Connectivity
Principal Investigator: Dr. Emily Sharp
Co-Principal Investigator: Elizabeth Togneri
Affiliation: Yale University School of Medicine, Connecticut Mental Health Center, & Cornell Scott-Hill Health Center

Invitation to Participate and Description of Project

We are inviting you to participate in a research study designed to look at change in depression severity and brain activity following three different interventions. You were selected because you are currently undergoing pharmacological treatment for depression. Approximately 213 individuals will participate in this study. Every individual will be randomized to one of three groups: Sudarshan Kriya Yoga (SKY) breathwork alongside antidepressants, Mindfulness Based Stress Reduction (MBSR) with antidepressants, or only continuing antidepressants. Change depression symptom severity as well as brain functional connectivity via fMRI scans will be compared amongst these groups after 8 weeks.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This permission form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to participate in this study, you will be asked to undergo an fMRI scan both prior to the start of the study and at the conclusion of the study at approximately 8 weeks.

After signing the consent form, you will be contacted by a researcher to complete two surveys. One will be completed on your own time and is called the Beck Depression Inventory, Second Edition. A second survey will be administered by a clinician who will ask you a number of questions concerning your depression which is called the 17-Item Hamilton Depression Rating Scale. Both surveys will be completed again at the conclusion of the study.

You will also be randomized into one of the three aforementioned groups. All group participants will continue their current antidepressant regimen per usual. If you are assigned to the first group, you will be instructed in basic breathwork skills according to Sudarshan Kriya Yoga (SKY). If you are assigned to the second group, you will participate in meditation sessions according to Mindfulness Based Stress Reduction Protocol and also continue your antidepressant regimen. If you are assigned to the third group, you will only continue your antidepressant medications. You will be sent a confidential, password protected link to participate in online training for either group which has an additional treatment, either breathwork or mindfulness skills.

If you are randomized to the Sudarshan Kriya Yoga group, you will have one 2.5 hour session led by a certified instructor during Week 1 who will teach the basic breathwork skills. You will then be expected to practice breathwork 45 minutes per day, six days each week. Lastly, you will attend a 7.5 hour workshop during Week 6, also held online. If you are assigned to the MBSR group, you will undergo the same time commitment as above, but be taught by a different instructor who specifies in full body scan practice, sitting meditation, and Hatha yoga.

The purpose of this survey is to evaluate whether nonpharmacological adjunctive treatments can improve depression severity and alter functional connectivity in the brain.

If research results are published, your name and other personal information will not be given.

Risks and Inconveniences

Magnetic resonance (MR) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of different parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines.

You will be watched closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you have them.

There are some risks with an MR study for certain people. If you have a pacemaker or some metal objects inside your body, you may not be in this study because the strong magnets in the MR scanner might harm you. Another risk is the possibility of metal objects being pulled into the magnet and hitting you. To lower this risk all people involved with the study must remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a

detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once you are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

We want you to read and answer very carefully the questions on the MR Safety Questionnaire related to your personal safety. Take a moment now to be sure that you have read the MR Safety Questionnaire and be sure to tell us any information you think might be important.

This MR study is for research purposes only and is not in any way a healthcare examination of the brain. The scans performed in this study are not designed to find abnormalities. The principal investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a healthcare evaluation of the images. If a worrisome finding is seen on your scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the principal investigator or consulting physician will contact you, inform you of the finding, and recommend that you seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie only with you and your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that you receive based on these findings. The images collected in this study are not a healthcare MR exam and for that reason, they will not be made available for healthcare purposes.

Recording daily MBSR meditation sessions and SKY breathwork sessions may come as an inconvenience to you. Researchers will be available for questions at any time and encourage your full participation.

You may be uncomfortable revealing personal information in participant surveys. Every effort will be made to keep your information confidential. A breach of confidentiality is unlikely to occur, as all study investigators are trained in research privacy.

Benefits

This study aims to evaluate whether depression severity can be further relieved by supporting individuals through breathwork or mindfulness based tactics. There may be direct benefit for you from participation in gaining a new skill and tool, whether it is breathwork or stress reduction techniques, to help with depressive symptoms. Your participation may also forward research to help many others also suffering from depression to find effective, additional therapy options.

Treatment Alternatives/Alternatives

Appropriate alternative options regarding therapy and diagnostic options include speaking with your primary care provider or psychiatrist regarding current medication dosages, as well as declining to participate in this study.

Confidentiality

We understand that information about your health is personal, and we are committed to protecting the privacy of that information. Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State Law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Information will be kept confidential by using identification numbers on study forms, storing signed forms in locked cabinets and password protecting data stored on a computer. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific permission for this activity is obtained.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All healthcare providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine are required to comply with HIPAA and to ensure the confidentiality of information.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. This will cancel any future MRI appointments and evaluation of depressive symptoms based on surveys. To withdraw from the study, you can call or email a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with the Connecticut Mental Health Center and the Cornell Scott-Hill Health Center.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject:_____

Signature:_____

Relationship:_____

Date:_____

_____ _____

Signature of Principal Investigator Date

or

_____ _____

Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Co-Principal Investigator, Elizabeth Togneri.
If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

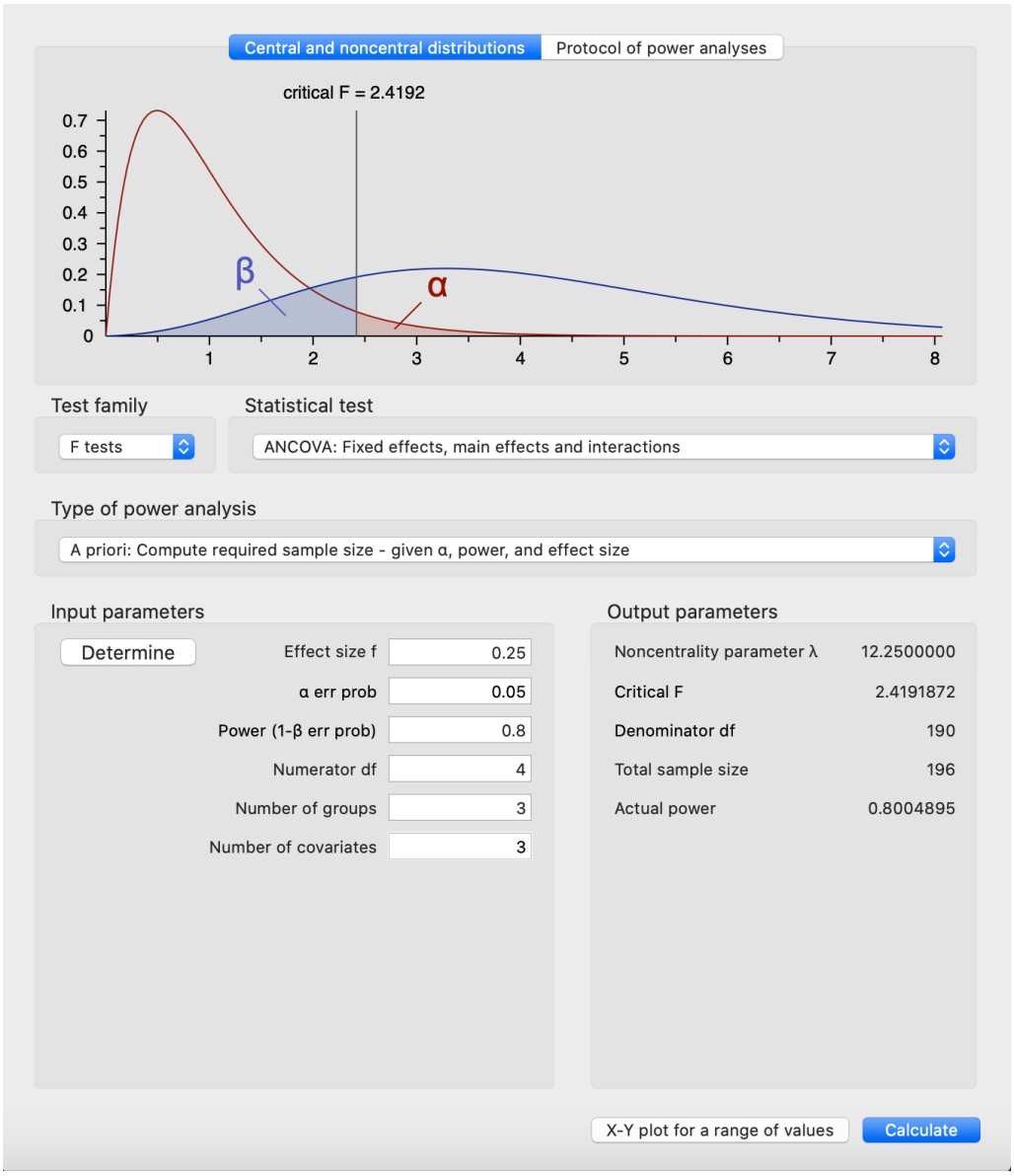
Appendix H: Sample Size calculation

The sample size was calculated* using the following parameters

Alpha= 0.05 (2-sided hypothesis)

Power= 0.80

Factoring in a 10% drop-out rate, the final sample size is 213, with 71 individuals per group.



*Calculated using G*Power version 3.1 with ANCOVA

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