A. SPECIFIC AIMS

Use of complementary and alternative medicine (CAM) modalities increased almost 50% from 1990 to 1997 [1]. Meditation is a commonly practiced CAM modality by both patients and physicians [1, 2]. One extensively researched practice is Transcendental Meditation (TM), a simple, mental technique practiced by millions of people worldwide, of diverse ages, cultures, religions and socio-economic groups [3]. TM's many physiological and psychological benefits have been documented in over 125 studies published in peer-reviewed journals [4-6]. Despite the strong evidence of its clinical effectiveness and continued federal funding for clinical trials employing TM, there is no empirically based, reliable and accurate model of brain mechanisms underlying TM or any meditation practice [7-12]. This lack is primarily due to the fact that the models are based primarily on electrophysiological and physiological data, which allow only indirect inferences about brain mechanisms. To provide a more accurate and reliable model of this CAM modality, we will develop an imaging-based neural model of TM mechanisms. This research thus responds to the request of NCCAM's *Five-Year Strategic Plan* for basic neuroscience mechanism studies of meditation [13]. Systematic substate analysis of one meditation could provide CAM researchers a research methodology to investigate other meditation techniques. Thus, this research could provide an empirical framework for comparative research on the mechanisms of different meditation techniques, and facilitate application of meditation to various clinical populations, through increased appreciation of differential effects of various meditation practices.

Functional Magnetic Resonance Imaging (fMRI) provides a non-invasive technology for directly imaging brain blood flow in terms of blood oxygen level-dependent (BOLD) signal intensity [14]. This study uses fMRI to identify BOLD signals, reflecting changes in neural activity, associated with two principal substates of TM practice: (1) the onset and progression of de-excitation; and (2) the periods of maximum de-excitation. The temporal and physiological characteristics of these two substates fit the constraints of standard fMRI cycling and event- and state-related analyses. This R21 grant is a collaboration between Maharishi University of Management, Michigan State University and Henry Ford Hospital (Detroit). Our preliminary fMRI work resolved a number of initial design and feasibility issues, indicating that subjects can successfully practice TM in the fMRI environment, that the two substates can be subsequently identified using respiratory patterns, and that fMRI analysis can yield significant changes in BOLD signal intensity.

The results of this R21 research on TM practice will provide: (1) a carefully tested fMRI protocol; (2) determination of potential BOLD signal sources during two principal TM substates; and (3) a more accurate and reliable model of brain mechanisms during meditation. The results will support several R01 proposals, including detailed study of selected brain areas during meditation such as forebrain and brainstem autonomic and respiratory centers; verification on a larger subject population; and comparative meditation studies.

The seven hypotheses comprising the two Aims of this R21 grant are:

Aim 1: Initial De-excitation Meditation Substate. We predict that fMRI cycling protocol will yield a distinct spatial and temporal pattern of BOLD intensity, reflecting an overall decrease in brain excitation. We will test two hypotheses in this experiment.

(1) Epoch Length Hypothesis: We hypothesize that the shorter epoch length in a ABC-cycling protocol (randomly-ordered meditation and controls) will best 'frame' the initial de-excitation process due to significantly higher signal-to-noise ratio, higher signal intensity and less variance in the statistical test;
(2) Control Conditions Hypothesis: We hypothesize significant differences in signal intensity across the three different epoch conditions—TM, passive-attending and mental-counting. Specifically, de-excitation will be maximum for TM, then passive-attending, and lastly, mental-counting.

Aim 2: Maximum De-excitation Meditation Substate. We predict that event-related (er-fMRI) and state-related (sr-fMRI) analytic procedures will yield distinct spatial and temporal patterns of BOLD intensity that characterize the maximum de-excitation substate associated with spontaneous breath-quiescent periods (SBQ, breath period > 10 sec). We will test five hypotheses in this experiment.

(3) IBH-Blood Gas Hypothesis: Using event-related-fMRI, we hypothesize moderate changes in blood gas changes will be detected during Intentional Breath-Holding (IBH), and blood gas levels will be significantly correlated with changes in BOLD signal intensity, consistent with published findings.
(4) SBQ-Blood Gas Hypothesis: Using event-related-fMRI, we hypothesize small changes in blood gas changes will be detected during Spontaneous Breath Quiescence (SBQ), and blood gas levels will not be significantly correlated with changes in BOLD signal intensity.
(5) SBQ-IBH Hypothesis: Using event-related-fMRI, we hypothesize that specific spatiotemporal patterns of BOLD signal will be associated with onset of SBQ, and will differ from IBH control periods in terms of reduced BOLD signal of the anterior cingulate cortex and brainstem during SBQ.
(6) SBQ-Controls Hypothesis: Using state-related-fMRI, we hypothesize that BOLD signal intensity patterns during SBQ periods will differ from two control conditions—IBH periods, and eyes-closed periods (as defined in Aim 1, either passive-attending or mental-counting).
(7) SBQ-Non-SBQ Hypothesis: Using state-related-fMRI, we hypothesize that BOLD signal intensity patterns during SBQ periods will differ from the scans during non-SBQ periods during meditation.

B. BACKGROUND AND SIGNIFICANCE

B.1. Need for Basic Neuroscience Research on Mechanisms of CAM Modalities.

Although a growing body of biomedical research supports CAM efficacy, there are still major gaps in the CAM literature [15-18]. One such gap reflected in the NCCAM *Five-Year Strategic Plan* is the need for basic research to elucidate underlying mechanisms of CAM modalities [13]. This grant responds to this call by using fMRI to identify brain mechanisms during Transcendental Meditation (TM), a widely researched CAM modality [1, 19]. These findings should help provide an empirical framework for comparative research on the mechanisms of different meditation techniques, and facilitate implementation of meditation to various clinical populations, through increased appreciation of potentially differential efficacy of various types of meditation.

B.2. Rationale for Investigating Mechanisms of TM.

TM is an logical choice for a CAM basic mechanism study for the following reasons: (1) TM is ***easy to learn and practice*** making it a widely used form of meditation providing a large subject pool [3]; (2) its ***efficacy*** has been validated with a large body of research [4-6]; (3) the range and extent of ***benefits*** significantly differs from other forms of meditation and relaxation [19]; (4) research has delineated specific ***reproducible substates*** during TM practice [9, 20-22]; and (5) preliminary ***neural models*** exist providing a theoretical basis on which to construct more reliable models from neuroimaging data [8-11].

B.2.1. Description of the TM technique.

The TM technique is simple, mental procedure practiced for 20 minutes twice daily. [3, 23]. The standardized instruction for TM is simple, and it may be learned by almost anyone regardless of age, culture, socio-economic status, belief, motivation or intelligence. Millions of people have been taught TM in the U.S. alone. TM differs from most meditation practices because it involves neither contemplation, nor concentration [24]. The practice involves sitting comfortably with eyes closed and thinking a simple sound (mantra), whose effect is to facilitate the de-excitation of mind and body, without loss of awareness. During TM, the mind settles down in an effortless, automatic fashion, without need for control of thoughts, focus on any process, such as the de-excitation process, or attention to the body, breath or environment. The effortless nature of the de-excitation process appears to permit endogenous brain mechanisms to function without interference from the individual's mental state [8, 9, 22]. Thus, this mental procedure not only permits the onset of de-excitation process, but is also responsible for the reproducible appearance of both the de-excitation substate and the maximally quiescent substate in meditation.

B.2.2. Clinical effectiveness of the TM technique.

Mechanism studies are best conducted after clinical effectiveness has been established. This neuroimaging proposal grows out of 40 years of research on the TM technique. The clinical efficacy of TM benefits has been documented in over 125 research studies published in peer-reviewed journals [4-6]. TM is reported to reduce chronic stress [25-28], a major risk factor for chronic disease and unhealthy behaviors [29-33]. TM practice is associated with reductions in the incidence of cardiovascular disease [35], hypertension [34-37], high cholesterol [38, 39], and unhealthy behaviors such as smoking [40, 41] and substance abuse [42-44]. TM practice is also associated with improved psychological health, as reflected by reductions in anger, hostility, anxiety, depression, and low self-esteem [43, 45-47].

B.2.2.1 Meditation-specific vs. lifestyle-specific benefits. Research on clinical populations suggests that TM practice produces changes largely independent of lifestyle effects. For example, Alexander et al. [31, 48] found similar improvements in cardiovascular morbidity and mortality from TM practice in bothhigh- and low-risk populations. Thus lifestyle changes alone may be secondary to effects of regular TM practice. Recent research [37] examined the effects of a cardiovascular risk-factor prevention education program compared to TM practice on carotid artery intima-media thickness (IMT). At the end of 6 and 9 months, the TM group had significant decreases in IMT, while the education control group continued to show IMT increases. Given the results seen in CVD populations, we might expect to see significant mind/body changes primarily due to TM practice itself, in the general population.[42, 49-54]. The proposed study will contribute to the continued examination of this issue by developing an integrated neural model of the practice, which may help distinguish meditation-specific from lifestyle-specific effects

B.2.3. Comparison of TM practice to other meditations.

Clinical comparisons and statistical meta-analyses support the hypothesis that different techniques produce different outcomes [19, 55-59]. An analysis of 597 studies on different meditation and relaxation techniques [19] showed that TM had the largest intervention effect in five outcome categories compared to eyes-closed rest, other meditation techniques, and relaxation responses: reduction in trait anxiety, high blood pressure, substance abuse, enhancement in self-actualization and physiological relaxation [44, 60-63] [64]. Thus, the benefits of TM practice favorably compare to similar CAM modalities [19].

B.2.4. Delineation of Reproducible Substates of Meditation.

We consider it a key research strategy to conduct systematic substate dissection of a single meditation technique to enable researchers to adapt the research methodology to mechanism studies of other meditation techniques, and then carry out comparative studies. Objective research of meditation will require systematic comparative investigation of different types of meditation. Toward this end, the present dilemma is the paucity of published research on brain activity during meditation (especially neuroimaging), and the

existence of numerous forms of meditation to study [see, 65]. Furthermore, the TM technique appears to be the only meditation for which there is any empirical substate analysis published. Without substate analysis, comparative studies would be subject to considerable undefined variation in experimental parameters, reducing the ability to understand any given technique or a comparison across techniques. Thus, we have chosen the TM technique to carry out this neuroimaging substate analysis because of TM's (1) extensive research database, in particular, substate analysis; (2) existing neural model efforts [7-9, 22, 66-69]; and (3) strong effect size in clinical research, suggesting substate dynamics have beneficial consequences to mental and physical health [19, 60, 61, 70-72]. Also, the inclusion of more than one technique in a R21 format focused on substate delineation would compromise the sample and effect size.

B.2.4.1 Distinct, reproducible substates during TM practice. TM practice produces a set of distinct alternating substates rather than a single homogeneous physiological response [10, 20-22]. The principal two substates are: (1) the initial onset and progressive de-excitation in the first minute of practice and subsequently [9]; and (2) periods of maximum de-excitation, physiologically marked by spontaneous breath-quiescence (periods > 10 sec) and subjectively marked by reports of maximum inner quietness [10, 20]. Our intention is to conduct careful and systematic comparative research on meditation. As a pragmatic start, this mechanistic research proposal is focused on these two substates during the TM practice because: (1) these substates occur repeatedly during TM; (2) they are distinguishing features of the practice; (3) there is strong evidence to suggest that there will be distinct patterns of neural activity underlying each substate [9, 20-22]; and (4) these substates may be generalizable to other meditation practices [65].

B.2.4.2. Experimental verification of de-excitation substate. In Section D.5.1, we designed an experiment to "frame" the de-excitation process. The entire de-excitation process begins from the ordinary thinking level. With the start of the mantra or sound, thinking settles down and process ends with the distinct inner subjective experience of awareness without thoughts, correlated with SBQ. Preliminary research indicates that long, 60 second cycling protocols will include the entire de-excitation substate, ending with a SBQ [Arenander and Travis, unpublished research, 2001][9]. In the subject screening process, this long cycle time run will provide an initial estimate of the average time of transit for each subject terminated by SBQ. With this information, we can more accurately "frame" the de-excitation substate for each subject using shorter (20-40 sec) cycle periods. This will permit imaging of the de-excitation substate alone, without contamination with SBQ and any subsequent brain substates.

B.2.4.3. Summary of substate strategy. Progress in understanding brain dynamics of meditation and other CAM techniques will depend at least partially upon the elucidation of the temporal structure of physiological and psychological events during the practice [see, 65]. Previous EEG and autonomic research has begun to delineate distinct substates during TM practice [8-10, 22, 67, 69]. It is unlikely these substates are 'epi-phenomena,' but rather, are reproducible, essential brain states that comprise the practice of the TM technique. With the exception of TM and one other very rudimentary meditation model [see references in 65, 73], all meditation techniques lack an empirically defined temporal structure. This may be a considerable hindrance to progress in CAM research, as well as the clinical application and interpretation of meditation techniques. In this context, formulating a neural model of substates during TM practice could be the basis of understanding: (1) the immediate and long-term effects of TM practice, (2) how TM practice can benefit specific clinical groups, and (3) whether similar substates are found in other meditation techniques.

B.2.4.4. Precedence for substate research. Aserinsky and Kleitman published the first evidence of possible substates during a night's sleep in early 1950's [see, 74]. Their seminal article has led to over 50 years of major research efforts to describe the systematic and sequential unfoldment of sleep stages, their alteration in health and disease, their develop from the fetus to mature to old age, forebrain and brainstem mechanisms of waking/sleeping transitions, questions of active versus passive control of sleep, and, the contribution that sleep makes to physiological homeostasis and human development [see, 75, 76-83]. Likewise, delineating meditation substates could provide a more comprehensive understanding of CAM modalities and help define future strategies for researching meditation and other CAM modalities.

B.2.5. Neural modeling of the TM technique.

Neural models of TM, which span 35 years, differ in their emphasis of meditation substate and/or of brain systems. These models include, in chronological order: (1) Kanellakos's stress reduction model [84]; (2) Wallace's implication of the hypothalamic-brainstem reticular activating system [11]; (3) Stroebel and Glueck's implication of the limbic-hippocampal circuit [85]; (4) Arenander's neurocognitive model identifying the interaction between the internal inhibition system of the basal forebrain and the internal excitation system of the mesencephalic reticular formation in regulating the de-excitation of the thalamic-cortical system and physiology [7, 8]; (5) Elias, Guich and Wilson's hypothalamic GABA model [86, 87]; and (6) Travis and Wallace's proposed interplay between active, neurally-induced inhibition (frontal and basal forebrain circuits) and automatic threshold regulation via cortical-basal ganglia-thalamic circuits [9]. The variety of neural models of TM may result, in part, from experimental perspective of the researchers, as well as the inherent limitations of the indirect electrophysiological and physiological measures of brain function.

B.2.5.1 Neuroimaging impact on existing models. Non-invasive, 3-dimensional, whole-brain neuroimaging data more directly explores brain activity responsible for the various physiological and

cognitive changes during meditation and benefits that occur as a result of meditation practice. Imaging data could considerably accelerate the evolution of individual models and comparison between models. For example, fMRI neuroimaging of BOLD patterns may delineate constellations of brain areas selectively activated and/or deactivated during each meditation substate. It may also be possible to identify specific forebrain and brainstem areas that are selectively activated at the onset, during and at the offset of the two key meditation substates [8, 9]. If so, this will aid in evaluating and differentiating the various TM models, and hopefully, yield a single, robust integrated neural model of TM practice. In turn, a neural model of one meditation technique could be used to improve understand and explore other meditation techniques.

B.2.5.2. Impact of neuroimaging on the performance of the TM technique. The purpose of this research is to investigate substates of a candidate meditation with demonstrated clinical effectiveness, not use research findings to alter the nature of its practice. Although this research is expected to help CAM researchers better understand brain dynamics of meditation, we believe each tradition should decide whether or not this understanding offers criteria for changing its meditation practice [65].

B.2.5.3. Impact of neuroimaging on health care and medical disorders. A neural model could help critically evaluate the potential implementation of TM or other meditations to benefit particular psychological or physiological disorders. For example, based on research, many doctors already prescribe TM practice to their patients to combat stress-related disorders such as cardiovascular disease [34, 36, 37, 63, 88-94].A more comprehensive and detailed understanding of neural mechanisms of meditation may contribute toward a better understanding the neural mechanisms of cardiovascular health [95-100, 101.] A neural model of meditation may also identify meditation-induced changes in brain areas known to be associated with other disorders such as violent behavior [102-107] or attention-deficit hyperactivity disorder [108-110]. Increasing use of fMRI to identify neural markers of other chronic diseases also increases the potential impact of this research on health care and psychological and physiological disorders.

B.3. fMRI Technology and Neuroimaging of CAM Modalities.

B.3.1. Description of fMRI.

Neuroimaging techniques such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) provide 2- and 3-dimensional maps of brain processes during specific tasks [111-113]. However, at present, fMRI has a number of key advantages over PET [14]: (1) It is non-invasive since it does not require injection of radioactive material; (2) Time resolution is faster, on the order of seconds; and (3) Spatial resolution is finer, on the order of millimeters. Thus, unlike PET, fMRI experiments provide better resolution and can be of longer duration and repeated in the same subjects. In this context, fMRI methodologies are well suited to investigate the two substates: (1) Cycling methodologies (e.g., alternating 20 to 30 second epochs) can be used to investigate the first substate, and (2) Event-related and state-related methodologies can be used to investigate the second substate.

MRI yields anatomic maps based on the inherent differences in behavior of H_2O, fat and bone tissue when aligning with an applied magnetic field (called T1), and then returning to their original state over time (decay, called T2)[14, 114]. fMRI detects the inherent difference in response of oxygenated and de-oxygenated hemoglobin in a fluctuating magnetic field [14, 114]. This is called the Blood Oxygen Level Dependency (BOLD) effect. The BOLD signal comprises hemodynamic variations in blood flow, volume and oxygenation. Recent work shows that the BOLD signal correlates very closely with the local field potentials, i.e., the electrical potentials arising from dendritic activity, and not the firing patterns, of neuronal cells [115]. Therefore, it appears the BOLD effect may actually index the preferential use of glycolytic metabolism of glial cells recycling glutamate neurotransmitter pools to the neuronal cells [116], providing a indication of CNS function. Also, BOLD dynamics closely correlate with visual, auditory and somatosensory tasks; hand squeezing, finger tapping and other overt motor tasks; and cognitive tasks [see, 111]. Thus, it is reasonable to infer that fMRI could help explore the various brain activations during substates of meditation.

B.3.2. Neuroimaging of CAM modalities.

fMRI has been successfully used to investigate various CAM modalities. Acupuncture effects have been reported in cortical and subcortical areas [117-120], which suggest an interconnection among the brain, target organs, and peripheral acupuncture points [117]. fMRI research also suggests distinctive activation patterns during hypnotic states [121]. fMRI research on verbal [122-125], visual [126-131],and motor imagery [132] have shown activation of expected brain regions. These studies demonstrate fMRI's effectiveness in imaging brain dynamics of CAM modalities.

More, recently, neuroimaging studies using PET and fMRI have begun to investigate the issue of 'baseline' conditions in evaluating brain dynamics. There appears to be a continuum of arousal or vigilance along a sleep-waking continuum, with a unique role of the thalamus and prefrontal cortex in maintaining a 'resting' state in the brain [133-141]. Researchers have identified a distributed neural system that maintain a task-independent state of brain function, in particular, medial and ventral prefrontal cortex [137, 140]. Brainstem reticular formation, thalamus and anterior cingulate cortex are linked together and are activated during arousal and cognitive challenge. This non-specific arousal modulatory system [see, for example, 135] is expected to be de-activated during the de-excitation process of meditation, but not 'turned off' as in sleep or anesthesia, since awareness and the ability to respond to external stimuli remain intact during TM.

B.3.3. Neuroimaging of meditation.

To date, only four neuroimaging meditation studies have been published, and they illustrate the diversity in meditation practices and outcomes [73, 142-144]. The following table summarizes two of these studies. The table reveals distinctive changes in brain activity as a consequence of different meditation techniques.

Summary of Brain Imaging Studies of Meditation		
MEASURE	**PET- $H_2{}^{15}O$** (Lou et al., 1999)	**fMRI** (Lazar et al., 2000)
Meditation	**Yoga Nidra**	**Kundalini Meditation**
Meditation Type	**Contemplation**: four different forms, including concentration, guided imagery, & body awareness following verbal instructions	**Concentration**: intense focused attention primarily on breath, coupled to repetition of different sounds
Comparison Condition	**Attention external:** Passive listening to verbal instructions, no task, no attention on breath	**Attention internal:** Mental task of generating a list of animals, no attention on breath
fMRI Outcomes		
Global	No change	Not available
Specific	Activation of postcentral, parietal & extrastriate cortex, hippocampus, no prefrontal or cingulate change	Activation of putamen, mesencephalon, anterior cingulate, hippocampus
Late versus Early Periods	Not tested	Cortical activation slowly evolved, maximum toward end of meditation
Interpretation	Similar to REM with exception of no cingulate activation; less control; brain areas correspond to nature of task performed	Constant vigilance requiring prefrontal & parietal attentional networks with focused attention
Correlates	EEG showed increased theta band power, no change in alpha power	Reduced respiration, increased heart rate in some subjects
Benefits	None referenced	None referenced

These findings emphasize that different forms of meditation generate different subjective experiences and different brainstates. Since TM's technique, experience, and physiological outcomes (see Sect. B.2.1.-B.2.5) differs substantially from the four meditations researched, we expect that TM practice will yield significantly different patterns of brain activation [see, 19]. More importantly, substate analysis will examine the detailed temporal dynamics of meditation that should be useful in the comparative study of meditation.

B.4. Experimental Rationale.

This exploratory R21 CAM mechanism study will provide a direct examination of brain dynamics during TM by imaging two of its principal substates. In the first year of the grant, we will investigate subjects during the onset of the de-excitation phase of TM practice, using a cycling protocol (see Sect D.5. for details). In the second year of the grant, we will investigate subjects during periods of maximum physiological quiescence during TM practice, marked by spontaneous breath-quiescence (see Sect. D.6. for details). We will use event- and state-related fMRI approaches in the second year.

This research will address basic fMRI design issues needed to better understand the origin of meditation-induced changes in the BOLD effect: (1) the contribution to the measured MR signal intensity of physiological covariables like respiration and changes in CO_2; (2) presence and delineation of reproducible substates during the practice; (3) the proper choice of the comparison condition in cycling protocols; and (4) the influence of nonspecific, respiratory-induced BOLD effects during spontaneous breath quiescence on imaging specific, meditation-induced BOLD signal changes.

By generalizing state analysis and brain mechanisms to the study of other meditation techniques this project should contribute to CAM research in physiological mechanisms of meditation. R01 proposals will be submitted to focus research on selected brain areas during TM such as forebrain and brainstem autonomic, respiratory and arousal centers and to conduct comparative meditation studies.

C. PRELIMINARY STUDIES

C.1. Introduction

The Review Panel recognized the strength and integrative quality of the original research team, including the credentials and publication record of the PI. Over the last two decades, Drs. Arenander and Travis have used the tools of EEG, ERP and autonomic recordings to discriminate the physiological mechanisms of different states of consciousness [see, for example, 12].

C.1.1. Dr. Arenander.

Dr. Arenander studied at UCLA with many of the leading researchers working in the areas of corticothalamic functioning, basal forebrain physiology, and their interaction with the reticular activation system in the control of states of consciousness. This training laid the foundation of the neural model of TM

practice proposed in 1975 [see, 7, 8, 66] that integrated known cognitive and brain mechanisms. Dr. Arenander was a member of an International team from 1974-1975 that generated much of the first body of research on meditation, including the first reports of unique EEG patterns, including theta rhythms [145] and phase coherence [146], Hoffman-reflex [147], and spontaneous breath-quiescence as an physiological indicator of transcendental consciousness during TM [20]. After an extended sabbatical working with genetic control of brain development, Dr. Arenander returned to M.U.M. as Director of the BRI.

C.1.2. Dr. Travis.

Dr. Travis has extensive experience with EEG data analysis, conducting research on physiological correlates of cognitive function and brain control of states of consciousness. Since 1984, he has compared EEG patterns between non-meditating and meditating subjects. This research has resulted in publications that integrated meditation experiences and physiological correlates with models of waking experience. Recently, a series of papers have: (1) systematically compared TM to eyes-closed rest [9, 148-151]; (2) studied TM substates [10, 22, 152], and (3) investigated long term effects of regular TM practice [153, 154].

C.1.3. The Research Team.

The M.U.M. team's fMRI design and analysis expertise has substantially expanded over the years. With the guidance of Drs. Haller and Bollinger at the University of Iowa's Dept of Radiology, the M.U.M. team (1) designed the preliminary set of fMRI experiments and participated in the data acquisition; (2) established a working AFNI-based computer system at M.U.M. Neuroimaging Lab, and performed the fMRI data analysis; (3) conceived the proposed experimental design; and (4) wrote the grant application.

As stated in the Introduction, we have relocated the research site and team members from University of Iowa to Henry Ford Hospital in response to changes in the UI Department of Radiology. **We feel the new team with the MRI expertise from Henry Ford Hospital and Michigan State University is a stronger team.** Dr. Jim Ewing is Director of the Neurology imaging center, and Dr. Yue Cao, formerly with the HFH imaging center and now conducting fMRI research at Michigan State University. Strengths of the HFH imaging center include: (1) a 3T magnet, which provides higher resolution than the 1.5T at the UI Imaging Center; (2) the 3T GE software routinely scans 19 slices at a time (whole head) compared to 5 slices at UI; and (3) the 3T scanner can collect the physiological data necessary for this study. Strengths of the Michigan team members include: (1) more senior research faculty status; (2) extensive previous research collaboration; (3) extensive experience with fundamental issues surrounding MR imaging animals and humans; and (4) more research experience in applying event-related-fMRI analysis. The four team members have discussed this research proposal in detail during meetings at HFH and over the phone and we concur with the strategy and experimental design.

C.1.4. Institutional Interaction.

Our team has ongoing communication and site visits with fMRI neuroimaging laboratories at Stanford, University of California at Irvine, University of California at Los Angeles, University of Wisconsin at Madison, University of Indiana, Cornell Medical Center, and Washington University in St Louis. Communications with labs at UCLA, Stanford and Indiana that are actively researching respiratory dynamics has increased our understanding of possible confounds. For example, peripheral blood gas is the standard measure used to estimate covariance of the BOLD signal, as well as the changes induced during breath-holding. More importantly, all evidence to date indicates that respiratory-induced BOLD effects from breath-holding, are relatively diffuse and stable. These nonspecific BOLD effects appear to be additive to the specific BOLD effects of cognitive, sensory or motor tasks. Such reports support the efficacy of the experimental design.

C.1.5. Research Consultant.

As an adjunct to the research team and the expertise of Dr. Cao, we have included Dr. Todd Braver, as a consultant on this R21 (see letter of support and biosketch). We have visited with and discussed the neural and experimental issues involved in this proposal with Dr. Braver. Dr Braver (Psychology Department at WU at St. Louis) is a well-published cognitive neuroscientist who has considerable experience with both brain mechanisms and, more importantly, with er-fMRI [161-168]. In fact, Braver and Bruckner may be considered the central developers of the cognitive neuroscience application of er-fMRI analysis that is used by many of their colleagues at the Department of Psychology and a growing number of neuroscientists worldwide.

C.2. Preliminary Data

C.2.1. Rationale.

At the University of Iowa Magnetic Resonance Center, we conducted several fMRI sessions on two male subjects (age 53 and 55) with both cycling and free-running protocols. We studied a motor task as a positive control with a cycling protocol (alternating 45-sec periods of rest and task) and multiple TM cycling runs (alternating 45-sec periods of eyes-closed counting and TM) and non-cycling runs (5 mins continuous meditation). This preliminary study was undertaken to address possible concerns about the effects of fMRI environment on meditation experience, such as noise, supine position, and interruptions of a cycling protocol, and to gain experience in fMRI design, acquisition and analysis.

C.2.2. Pretest protocol.

Prior to fMRI runs, subjects practiced meditating at home in a supine position (in constrast to normal upright sitting position) with a audio recording of fMRI noise. Subjects came to the M.U.M. lab and did a 'dry'

run in a fMRI machine mockup with audiotape to simulate the actual run experience (noise, claustrophobia, etc.). Physiological markers were recorded and the signaling paradigm between the subject and the experimenter was tested (use of audio vs. light beam signals). Subjects filled out consent forms at M.U.M. and UI before testing. Following selection procedures, subjects went to the UI MR Center for testing.

C.2.3. Acquisition Protocol.

Subjects were reminded again of the nature of the experiment and signaling protocols. Following setup and positioning in the scanner, we acquired standard anatomic scans lasting about 40 minutes before experimental scans. The anatomic scans included: (1) a T2-weighted sagittal localizer using a fast spin echo sequence (TE/TR 100/4500; 24 5mm slices; 2mm space; 256X224, NEX2 1:30); and (2) a volumetric scan (3D RF-spoiled gradient echo sequence with TE/TR 7/26 ms; 256X192 matrix). Experimental scans included (1) a 2D T1-weighted scan of the slices to be acquired in the fMRI study (2D RF-spoiled gradient echo sequence with TE/TR 7/26ms), and (2) an 8-shot EPI sequence of the slices to be acquired (TE/TR 40/3000 ms). The 8-shot EPI sequence and T1-weighted slices are used to align the fMRI data with the volume scan. For fMRI studies, we used the EPI sequence with 128 by 128 data acquisition matrix, TE of 40 msec, TR of 3 sec, FOV 24 cm, slice thickness of 5 mm. Since fMRI was conducted on a single slab (software limitation of the 1.5T GE scanner system), we initially chose a slab (5 slices, 118 degree angle) that traversed regions of greatest interest (see figure 1A): progressing from anterior/superior to posterior/inferior, the regions of interest included the prefrontal cortex (anterior polar, dorsolateral, ventromedial and rostral anterior cingulate), the basal forebrain and hypothalamus, the thalamus, the mesencephalic brainstem and the cerebellum. We were aware of the possibility of tissue ghosting.

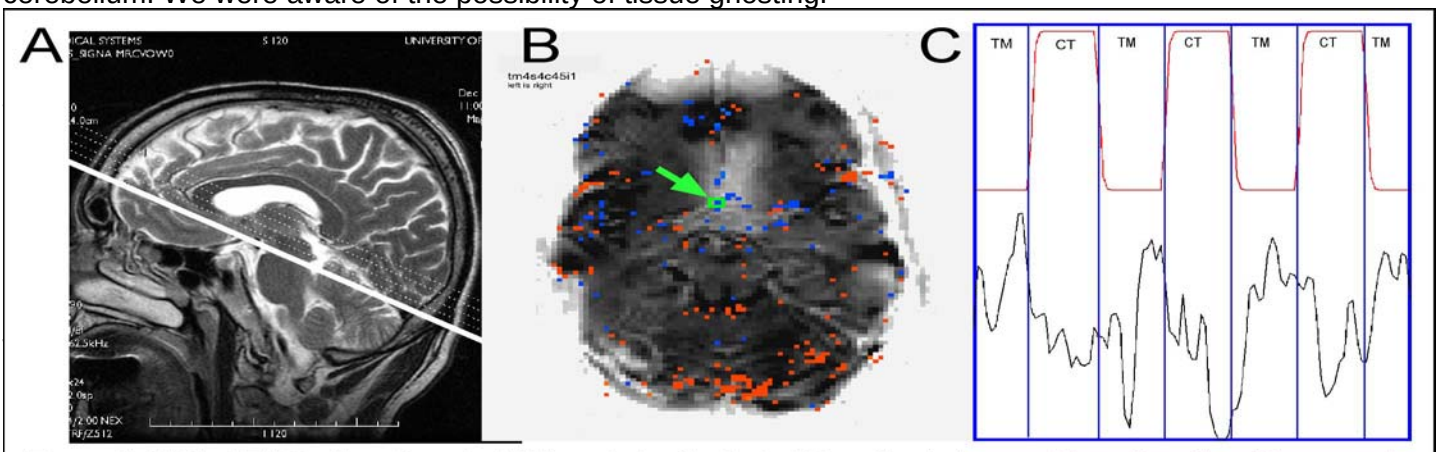

Figure 1. fMRI of TM Cycling Run: An AFNI analysis of a 5-min TM-cycling task comprising alternating 45-sec epochs of TM practice and comparison task (eyes-closed mental counting by 2's). (A) The location and orientation of a brain slice. (B) The fMRI scan of this slice with the correlational analysis superimposed as colored pixels (correlation threshold = 0.45). A number of regions distributed across the brain slice display pixels indicating increased (blue) or decreased (orange) signal intensity. (C) Graph plotting the signal intensity over the 5-min cycling run for the pixel located in the basal forebrain noted by the arrow (TM, meditation epoch; CT, control task epoch). This picture is meant to convey the functionality of our acquisition and analysis system. Since the data is from only a single run one cannot draw any specific significant conclusion regarding neural change associated with the cycling. In addition, this subject has considerable artifact (grey areas signify signal dropout) often seen in ventral slices due to dental work and/or air-bone interfaces. (Color copies in Appendix; *R21, fMRI Study of Brain Mechanisms during Meditation*).

constructed a map of the correlation of the task-reference function with the corrected fMRI images. The task-reference function is created by convolving a standard hemodynamic response function—a gamma variate function with parameters described by Cohen [170] on the time series of the boxcar design of 0's and 1's. The results are displayed based upon a chosen level of significance, as either response time series maps for scans across each epoch and the entire run, and anatomic image overlayed with pixels possessing significant (positive or negative denoted by color) correlation. Data from the few noncycling runs were analyzed but did not have sufficient SBQ periods to yield reliable comparisons. One subject had very few (and very short) SBQs and the other subject had very few SBQs. The noncycling runs were conducted last in the early protocol and after a considerable period of lying in the scanner. Subject selection in this application will maximize for the number of individuals with SBQs in both cycling and noncycling runs.

C.2.6. Results of Cycling Runs.

C.2.6.1 Successful Practice of Meditation: The study clearly demonstrated that subjects were able to meditate during the fMRI recording as indicated by self-reports of the normal range of meditation experiences, and the presence of multiple spontaneous breath-quiescent periods, indicative of the reoccurrence of both substates during TM practice: the process of de-excitation and the most de-excited substate corresponding to SBQ.

C.2.6.2 System Functionality: The study demonstrates the collaborative effort could yield images of task-dependent significant BOLD intensity changes. Serving as a positive control for the functionality of the overall system, the motor task revealed increased signal intensity localized over the motor cortex representation of the hand (data not shown). Significant pixels appear with little background noise within a few cycles. By the end of the motor run, a clear overlay of the cortical area was evident, as expected.

C.2.6.3 Significant BOLD Effect in Meditation: Analysis of the TM cycling-task revealed significant changes in BOLD signal intensity in a number of discrete cortical and subcortical areas during TM practice (See Figure 1). Figure 1 presents three graphic outputs from the AFNI analysis: **Fig (1A)** a sagittal view MRI image indicating the 5-slices slab recorded; **Fig (1B)** the fMRI image of the bottom slice (with normal spatial distortion) along with an overlay of the correlation map of the relation of signal intensity with the task-reference function; and **Fig (1C)** the time series graph of the change of signal intensity across a representative 5-min cycling run. We hesitate to interpret the general significance or meaning of pixels that are displayed as significantly correlated. In fact, the figure is meant to convey the ability of the research team to carryout a fMRI run from acquisiton to analysis, and not intended to display evidence or proof of any general or specific prediction as to possible activation/deactivation patterns. The figure was the outcome of training of the M.U.M.-based investigators by the UI researchers. It suggests a functional imaging analysis system at M.U.M. capable of carry out the aims of the proposal. Furthermore, the data displayed should not be extrapolated, since it is (1) from a single cycling run, (2) on a single subject, (3) using subtraction from only one possible control condition (eye closed counting), (4) uncontrolled for substate mixing known to occur based on respiratory patterns (sequences of de-excitation, SBQ and post-SBQ substates), and (5) displays obvious tissue inhomogeneity artifact. Since the cycling was a derived from multiple TM (and control) periods which differed significantly in substate composition based upon respiratory pattern and self-report, any significant pixels (positive or negative) represent an averaging across at least two substates of varying duration. For example, the displayed clusters in basal forebrain and cerebellum thus, do not necessarily represent the de-excitation process alone. In the face of substate mixing, it is noteworthy that relatively robust intensity changes endure. This suggests that a properly framed de-excitation should yield specific measurable patterns of BOLD intensity change. Although the preliminary data disallow any reliable conclusions regarding neural patterning, it does illustrate both the ability to acquire and analyze data and the need to be careful in designing the experimental protocol.

C.2.7. Implication of Findings.

These results were used to design an experimental neuroimaging strategy relevant to carrying out a systematic, detailed examination of meditation dynamics. The proposal addresses a number of important issues derived from our preliminary study and consideration of the literature. These include the necessity of determining: (1) the optimal epoch length and appropriate comparison condition for TM cycling protocol; (2) the spatial distribution of meditation-induced BOLD effects in the brain; (3) the appropriate experimental protocol and statistical analysis methods to probe substates during TM; and (4) the contribution of physiological covariables on the BOLD signal during meditation. This later issue is further addressed by experiments that examine the degree to which the respiratory-induced and meditation-induced BOLD signal changes are independent and separable during the periods of spontaneous breath quiescence.

C.2.8. Summary of Preliminary Research.

We conclude that neuroimaging of meditation is possible and that significant information can be obtained by directly analyzing brain dynamics of two principal substates that have been described by previous research utilizing only indirect measures [9, 20-22]. These two mediation substates are: (1) the progressive de-excitation phase of TM practice, and (2) subsequent periods of maximum physiological quiescence during TM practice, marked by spontaneous breath-quiescence (SBQ, breath periods > 10 sec). We will investigate the first substate in Year 1 and the second substate in Year 2.

D. RESEARCH DESIGN AND METHODS

D.1. Introduction.

This R21 exploratory grant will be carried out in collaboration with the Brain Research Institute's Neuroimaging Laboratory at Maharishi University of Management, Michigan State University and the Neurology NMR Facility at Henry Ford Hospital in Detroit. The grant will be devoted to imaging two principal substates during TM practice that are well-suited to fMRI recording and analysis.

The *first* principal substate that will be examined is the period of de-excitation at the onset of TM practice. This substate is well suited for a fMRI cycling paradigm because it occurs within the first 20-40 seconds of a TM session [9, 146]. A three component (ABC) cycling protocol with short alternating epochs (20 to 40 sec) of TM practice and two control conditions should allow 'framing' of this initial de-excitation process of meditation—sequentially turning it on, and then off. The experiment will determine: (1) the optimal

epoch length to capture the initial de-excitation process of meditation, and (2) the optimal comparison condition for this substate to use in a fMRI analysis.

The *second* principal substate that will be examined are periods of spontaneous breath-quiescence (SBQ), with a typical duration of 10-40 seconds. Periods of spontaneous breath-quiescence (SBQ) can occur many times in a meditation session. This distinct substate of breath-quiescence correlates with the distinct inner subjective experience of awareness without thoughts [10]. This substate can be probed with: (1) event-related fMRI methodology (similar to event-related potentials in EEG research) [171-177], and (2) state-related fMRI methodology [178]—binning (grouping by category) images from periods before, during and after this substate, and statistically comparing the three periods with multiple linear regression. This experiment will allow examination of brain BOLD dynamics of: (1) intentional breath-holding and (2) SBQ.

The nature of the respiratory confound in imaging meditation is a central issue. This confound should not affect the first phase (Aim 1), which investigates the initial de-excitation substate of meditation, because this substate occurs with little change in respiratory variables or alterations in blood gas levels [9, 22, 179]. However, the second phase (Aim 2) may be confounded by respiratory-induced BOLD effects, since we are imaging SBQ periods. However, in the last three years, published studies of task experiments show that nonspecific, respiratory-induced BOLD effects do not mask the detection of specific, task-induced fMRI patterns [personal communication, Li, Glover, Moseley, & Harper, 2001][155, 156, 159, 160, 180].

D.2. Standard fMRI Acquisition and Analysis Protocol.

D.2.1. Data acquisition.

We will acquire standard anatomic scans during an initial 40 minutes period before experimental scans. The anatomic scans include: (1) a 3 plane localizer using a fast gradient echo sequence (TE/TR 1.7/32.1 ms); (2) a volumetric scan (3D Fast RF-spoiled gradient echo sequence with TE/TR 3.7/9.1 ms); (3) a 2D T1-weighted FLAIR scan of the slices to be acquired in the fMRI study (2D fast spin echo sequence with TE/TR 7/26ms), and; (4) an 8-shot EPI sequence of the slices to be acquired (TI/TE/TR 860/5.9/1977 ms). The EPI sequence and T1-weighted slices are used to align the fMRI data with the volume scan. For fMRI studies, we currently use the product EPI sequence with 64 by 64 data acquisition matrix, TE of 30 ms, TR of 2.2 sec, FOV 24 cm, slice thickness of 5 mm. 19 slices are acquired in an interleaved fashion (odd first, then even) for the entire time the paradigm is being performed. Following these standard MR scans subjects will perform a simple motor task cycling run (alternating 45 sec episodes of rest and hand-squeezing). This run represents a positive control for the cycling acquisition and analysis in every run.

D.2.2. Data analysis.

The HFH fMRI facility possesses real time fMRI acquisition and analysis software. Dr. Cao [181-183] has developed software for er-fMRI analysis [see also 168, 172, 173, 178]. A data analysis system, similar to the system at MSU/HFH, will be installed at M.U.M. This system will complement the AFNI system already running. The HFH software acquires fMRI images and other physiological data (pulse oximetry, respiration, electrocardiogram) on the same computer, allowing a synchronized time-stamp on all data sets. Each channel of acquired data contains a corresponding data file and a timing file. The time series from these other physiological variables will be used as real-time covariables in multiple linear regression, thereby statistically controlling for the contributions of breath rate and CO_2 to the overall BOLD effect.

The sequence of analysis includes: (1) discarding the initial three scans of each run due to magnetic instability; (2) correcting for movement artifacts by the co-registration of the time series using AIR (automatic image registration); (3) morphing the distorted fMRI image onto the accurate, high resolution MRI anatomic image, by registering fMRI images to the 8-shot EPI scan using AIR and registering the T1-slice to the 3D-volume using image intensity; (4) generation of statistical parameter maps from the *t*-statistics resulting from the multiple linear regression—a statistical parameter map (SPM) is a map of all pixel areas that exceed a specified statistical threshold and; (5) transforming the *t*-statistic maps into *Z*-statistic maps for statistical analysis. With large numbers—100 or more—the *t*-distribution approximates a *Z*-distribution [184]. These final statistical parameter maps will reflect significant fluctuations in signal intensity during the two conditions of the cycling tasks, after the contribution of other physiological variables have been statistically removed.

D.2.3. Statistical analysis.

One of the valuable characteristics of fMRI is that the relatively high signal to noise ratio allows detection of significant changes in signal intensity *within* a single subject [185]. The steps for statistical analysis of all data will include:

(1) The SPM [184] for the runs in each condition will be examined. Areas of significant signal fluctuations will be determined using two criteria [92]: (a) the *Z*-statistic > 4.0, ($p < 10^{-7}$), and (b) the cluster must contain a minimum of four pixels that touch on the sides or corners (eight-neighborhood connectivity).
(2) We will examine the first run for possible adaptation effects. If the first run differs significantly from subsequent runs, we will consider excluding the first run from the overall analysis.
(3) The *Z*-statistic of significant areas of fluctuations in signal intensity are noted when they meet the criteria above and are in 2 of the 3 statistical parameter maps from multiple runs in the same condition.
(4) These *Z*-statistics will be used in parametric analyses.

D.2.4. Sample size.

We determined the sample size of 10 subjects based on published studies [111, 186]. The fMRI study of Lazar et.a.l [143] reported significant results with five subjects. Two PET studies [142, 144] reported significant signal changes with nine and four subjects, respectively. The study of Qigong [187] examined cerebral blood flow using two subjects, but reported no estimates of significance. Newberg et.al. [73] neural SPECT study of Tibetan meditation reported significant blood flow changes with eight subjects. An examination of 50 reports on PET or fMRI imaging of various interventions, including CAM modalities, such as, hypnosis, acupuncture, complex cognitive tasks, or simple sensory and motor stimulation showed that statistical significance was found with 10 or less subjects [see for example, 108, 111, 162, 188, 189-199].

D.3. Timeline.

Over the two years, we will alternate between image acquisition and data analysis to sequentially address our two aims. At the conclusion of the R21, we will have delineated the basic fMRI methodology appropriate for imaging brain mechanisms during TM practice, and will have collected sufficient data to suggest a neural model of brain mechanisms underlying two distinct substates during TM.

Month	Activity Year 1	MRI Sessions
1	Upgrade Neuroimaging Laboratory at M.U.M. (new software and work station; Hire RA; Recruit subjects	—
2-3	Pre-screen and screen subjects; First runs to estimate effect size; Train RA to use analysis software at HFH and M.U.M.	**2**
3-12	**Aim 1—Expt 1:** Determine optimal epoch length and control condition during the cycling protocol	**18**
10-12	Write and submit papers	
	Total MRI sessions Year 1	**20**

Subjects will participate in multiple experiments (sessions).

Month	Activity Year 2	MRI Sessions
1-10	**Aim 2—Expt 2**: Determine BOLD response at the onset of and during intentional Breath-Holding and spontaneous breath-quiescence using er-fMRI and sr-fMRI analysis	**20**
10-12	Write and submit papers	—
12	Submit RO1s	—
	Total MRI sessions Year 2	**20**

The screening of 15 subjects will involve minimal recording time and analysis time. The recording time will be just over 1.5 hr for tests (a 5-min motor task cycling-run, TM cycling-runs, and uninterrupted self-paced TM runs) and 40 min for standard anatomic scans. The analysis will determine whether (1) the subject was able to meditate in the magnet as evidenced by breath changes and subjective reports, and (2) the fMRI images are relatively free of physiological and movement artifacts.

D.4. Population Selection.

The communities of Fairfield, IA and Greater Detroit, MI are uniquely suited for this study, with over 3,000 individuals who have been practicing the TM technique from a few months to over 30 years (average 10-20 years). This group ranges in age from 10 to over 80 years. We will attract 100 candidate subjects by email list and advertisement in Fairfield and Detroit. We will *pre-screen* potential subjects in Fairfield and Detroit, and then *screen* subjects with a trial run in the magnet in the HFH Neurology NMR Facility. Subjects will be reimbursed for participating in any of the five experiments detailed below.

D.4.1. Prescreening of subjects.

We will identify 30 subjects from the 100 candidates through the prescreening process, preferably from the Greater Detroit area (60 min driving distance). During pre-screening, subjects will learn about the nature of fMRI recording, the research design, and the inclusion/exclusion criteria. The criteria will be based on factors that may possibly affect measurement of BOLD activity:

(1) Basic demographics: (a) Age 20 to 55 years; (b) All right-handed (Edinburgh test of handedness); (c) English speaking; (d) No alcohol or cigarette use, and; (e) Similar number of men and women.
(2) Physiological: (a) No serious medical conditions; (b) No prescription medication; (c) No learning disabilities; (d) No history of head trauma; and (e) No metal within or on the body (including extensive dental work).
(3) Time: Subjects should be able to participate in the two experiments.
(4) Scanner: No claustrophobia and ability to meditate comfortably
(5) SBQ: Subjects should display SBQ at a rate of 10 per 20min of noncycling meditation.

D.4.2. Screening of subjects.

We estimate 30 subjects will meet the first three criteria. We will then assess medical history and obtain written consent (see Section E). They will be given an audio tape and instructed to practice the TM technique at home with earplugs, lying down in a darkened room, with the audiotape playing the fMRI machine noise. This home practice will accustom subjects to the fMRI experimental conditions. Then, subjects will come to either the HFH or M.U.M. laboratory for a trial run in a cardboard mockup of the MRI

machine with the same audiotape. In the mockup, subjects will practice TM, train with the signaling protocol, with both control conditions (passive listening and mental-counting), and have respiratory and autonomic data acquired, to satisfy the fourth criteria above. Subjects will pass this last two pre-screening criteria, if they are comfortable with the environment and protocol, and demonstrate clear periods of spontaneous breath-quiescence during the trial run. We estimate 20 subjects will qualify for MR imaging.

Of the 20 candidates, we expect about 5 individuals will not meet the final two criteria necessary for inclusion in the study during the first MRI scan at HFH. These two criteria are:

(6) MR protocol criteria: (a) No claustrophobia; (b) No metal placements within or on the body (including extensive dental work); (c) Minimal recording artifacts (e.g., low levels of head movement and tissue inhomogeneity, due to sinus configuration and dental work).

(7) Meditation criterion: Appropriate meditation experience based on subjective reports and respiratory patterns during TM practice in the MRI environment.

We expect that a minimum of 15 subjects will meet the full set of screening criteria and will be the subject pool for the five experiments in this grant. One of the advantages of running the same subjects multiple times is that within- and between-subject variance can be assessed.

D.4.3. Estimation of Sample Size.

We determined sample size of 10 subjects based on published neuroimaging studies [111, 186]. The fMRI meditation study of Lazar et.al. [143] reported significant results with five subjects. Two PET studies of meditation [142, 144] reported significant signal changes with nine and four subjects, respectively. Litscher's recent study of Qigong [187] examined cerebral blood flow using two subjects, but reported no estimates of significance. Newberg et.al. [73] neural SPECT study of Tibetan meditation reported significant blood flow changes with eight subjects. An examination of 50 reports on PET or fMRI imaging of hypnosis, acupuncture, complex cognitive tasks, or simple sensory and motor stimulation showed that statistical significance was found with 10 or less subjects [see for example, 108, 111, 162, 188, 189-199].

D.5. Examine the Patterns of Neural Activity during the De-Excitation Substate (Aim 1).

Experiment 1: Selection of epoch length and control condition to image the de-excitation process.

D.5.1. Hypotheses. We will be testing two hypotheses in this experiment.**D.5.1.1 Epoch length**. We hypothesize that the shorter epoch length in a ABC-cycling protocol (randomly-ordered meditation and controls) will best 'frame' the initial de-excitation process due to significantly higher signal-to-noise ratio, higher signal intensity and less variance in the statistical test;

D.5.1.2. Control conditions.We hypothesize significant differences in signal intensity across the three different epoch conditions—TM, passive-attending and mental-counting, including in rank order: de-excitation will be maximum for TM, then passive-attending, and lastly, mental-counting.

D.5.2. Issues.

D.5.2.1. Epoch length. Epoch length will be pre-framed during our subject selection protocol. We will examine two epoch lengths centered on this preliminary value. The best frame will include maximum duration of the de-excitation process without the actual onset of a SBQ for most of the meditation epochs.

D.5.2.2 Control conditions. Control conditions are an essential component of fMRI cycling. Since cycling runs yield a comparison of change in signal intensity between conditions, e.g. rest versus hand-squeeze or controls versus TM, it is important to carefully choose the comparison condition. The comparison condition ideally should differ along the dimension that best distinguishes the experimental task. Eyes-closed rest (without task instruction) would seem to be an appropriate comparison condition. However, during "rest" there is no control over the subject's cognitive processes. He/she could be daydreaming, engaged in intellectual or emotional mentation, drifting to sleep, or unintentionally settling into TM practice.

To avoid this confound, we will use an 'ABC' cycling protocol, comprising eyes-closed, randomly ordered epochs of (A) TM, (B) passive-attending to nature sounds, and (C) mental-counting by '2s'. Both controls minimally engage the subject attention, yet should help prevent them from either settling into meditation or drifting asleep, which can occur during simple eyes-closed rest condition. Counting is similar to TM in that both these eyes-closed conditions involve simple repetitive mental activity. Counting differs from meditation along a salient cognitive dimension—counting requires vigilance and attention to the counting process, while during TM practice, the attention automatically follows the thought process during de-excitation [3]. However, the counting-by-2's may activate specific brain areas. Eyes-closed mental arithmetic (reciting single digit multiplication tables and serial subtraction) has been found to activate pre-motor, frontal and parietal cortical areas [200]. We assume counting by 2's will not be as difficult a task as the above multiplication and subtraction. They require extensive activation of frontal areas that play an executive role in utilizing the semantic memory of arithmetical facts. The second control--eyes-closed passive-attending to audiotaped nature sounds--may more closely match the meditation cognitive dynamics of de-excitation. The primary difference being that in meditation the attention is moving in an 'inward' direction (effortlessly attending to internal experience) in comparison to the passive-attending control in which the attention is more 'outwardly' directed (i.e., listening to external stimuli). In conclusion, it will be important to compare the effects of passive-attending and mental-counting on fMRI during TM cycling runs.

D.5.3. Method.

We will record fMRI (in first 10 subjects meeting inclusion criteria) during randomly ordered epochs of controls and TM practice. We will use two cycling ABC-run with eyes-closed. Each ABC-run comprises TM and two control conditions: (1) listening passively to nature (ie, ocean) sounds or (2) mental-counting by '2s'. An ABC-run (for example, using 30 sec epochs) will last about 22min, including 45 total epochs, 15 epochs each condition. This will result in 22 min/run x two epoch lengths = 45 min of testing, plus 40 min of preliminary anatomic scans, for a total time of less than 2 hr per MRI session. Whole-brain scans will be recorded from 19 slices per scan. At the end of each 22-min run, subjects will be asked to report their experiences. Carryover effects will be minimized by: (1) inserting one minutes breaks between runs. During these breaks we will be speaking and de-briefing the subjects; and (2) randomly presented control conditions in the same run. With this design, *within*-sets comparison will provide an estimate of the *minimal* carryover effects and *across*-sets will provide an estimate of *maximal* carryover effects.

D.5.4. Analysis for Hypotheses 1 & 2.

The data will be processed, and clusters of significant fluctuations in signal intensity will be noted (see Sect. D.2.2-D.2.3.). We expect clusters of fluctuations in signal intensity in 4-8 brain areas (see Sect. B.). The *Z*-statistics for areas of significant fluctuations in signal intensity will be noted from all runs and used as the variate in a repeated measures MANOVA. In this MANOVA, brain areas (4-8 estimate), and epoch condition (3) will be the factors, and the epoch-lengths (2) will be the repeated measure. For all main effects, individual comparisons will be conducted.

1. We expect **main effects for brain areas**, indicating significant differences in signal intensity between one or more brain areas. These changes may include in rank order: basal forebrain increases, slight cerebral and cerebellar cortex and mesencephalic reticular formation decreases, and no decreases in medial thalamus.
2. We expect **main effects for epoch condition**, indicating significant differences in signal intensity across the three different conditions—TM, passive-attending and mental-counting. These changes may include in rank order: de-excitation will be maximum for TM, then passive-attending, and lastly, mental-counting.
3. We expect **main effects for the repeated measures**, indicating the epoch length that best framed the initial de-excitation of TM practice. For example, longer epoch lengths run the risk of introducing new, and variable cognitive and brain processes. This variability could result in lower signal-to-noise ratio, low signal intensity and more variance in the statistical test.
4. We expect **significant epoch length x epoch condition interactions**. We expect less cognitive and brain variability in the shorter epoch length regardless of condition resulting in greater distinction between epoch conditions. On the other hand, the greater variability of the longer epoch length may diminish the measured difference in signal intensity between conditions.

D.5.5. Outcome.

At the conclusion of this analysis, we should have empirical data sufficient to recommend the epoch length and the control condition to successfully image the initial de-excitation substate of TM practice. Secondary outcomes include consistency of signal intensity for regions of interest within subjects, and variability across runs between subjects. Anatomically, based on previous research-driven neural models (see Sect. B.2.5.), we would expect to at least find cortical de-excitation with possible exceptions of medial and ventral prefrontal cortices, accompanied with some basal forebrain, basal ganglia and brainstem excitation, cerebellar de-excitation and no change in medial thalamic activity.

D.5.6. Conclusion of Aim 1 Experiment.

From this experiment, we expect to find four basic outcomes regarding brain mechanisms during meditation from an ABC-cycling protocol:

(1) The epoch length that appears to best frame the de-excitation process;
(2) The effects of two different control conditions;
(3) The brain areas that appear most closely correlated with the de-excitation process, as measured by the ABC-cycling protocol; and
(4) The intra- and intersubject variability of activation/deactivation patterns;

Collectively, these findings will help formulate a working model of brain mechanisms during the de-excitation substate of TM practice.

D.6. Examine the Patterns of Neural Activity during the Maximum De-Excitation Substate (Aim 2).

Experiment 2: Comparing BOLD patterns across periods of differing mental & blood-gas conditions

D.6.1. Hypotheses. We will test five hypotheses in this experiment.

D.6.1.1 IBH-Blood Gas Hypothesis. Using event-related-fMRI, we hypothesize moderate changes in blood gas changes will be detected during Intentional Breath-Holding (IBH), and blood gas levels will be significantly correlated with changes in BOLD signal intensity, consistent with published findings.

D.6.1.2 SBQ-Blood Gas Hypothesis. Using event-related-fMRI, we hypothesize small changes in blood gas changes will be detected during Spontaneous Breath Quiescence (SBQ), and blood gas levels will not be significantly correlated with changes in BOLD signal intensity.

D.6.1.3. SBQ-IBH Hypothesis. Using event-related-fMRI, we hypothesize that specific spatiotemporal patterns of BOLD signal will be associated with onset of Spontaneous Breath Quiescence (SBQ), and will

differ from IBH control periods as marked, in particular, by reduced BOLD signal of the anterior cingulate cortex and brainstem during SBQ.

D.6.1.4. SBQ-Controls Hypothesis. Using state-related-fMRI, we hypothesize that BOLD signal intensity patterns during SBQ periods will differ from two control conditions—IBH periods, and eyes-closed periods (as defined in Aim 1, either passive-attending or mental-counting).

D.6.1.5. SBQ-Non-SBQ Hypothesis: Using state-related-fMRI, we hypothesize that BOLD signal intensity patterns during SBQ periods will differ from the scans during non-SBQ periods during meditation.

D.6.2. Issues.

The second phase of the grant will systematically explore neural patterns underlying the second principal substate during TM practice—periods of SBQ with durations of 10 to 40 sec—signifying the maximum de-excited state of TM practice. A study of breath-quiescence raises a number of possible confounds.

D.6.2.1. Blood gas confounds.Quiescent breath periods can lead to significant changes in CO_2 [95, 201, 202] concentrations. In turn CO_2 changes can lead to alterations in brain blood flow [155, 203]. Therefore, it is important to monitor and determine the contribution of CO_2 changes to the measured signal intensity variation in our experiments on spontaneous breath-quiescence. To monitor CO_2, a Novametrix CO_2 monitoring system (Model #715 Capnograph with Pulse Oximetry) will be purchased in Year 2. This system will be used to sample breath via nasal cannula, which will provide O_2 saturation and endtidal CO_2 concentrations. These gas measures will be used as covariables in multiple linear regression. The resulting statistical parameter map will provide a more accurate picture of the *neural* mechanisms that are more directly responsible for generating or maintaining these quiescent periods.

Spontaneous breath-quiescence periods resemble, at least superficially, voluntary breath-holding periods, although they may differ considerably in origin. Most spontaneous breath-quiescence periods begin with an expiration. fMRI research indicates that breath-holding after expiration can lead to a fairly well defined BOLD pattern: a simple monophasic increase in response to respiratory 'suspension' [156, 157, 203-206]. This BOLD increase is diffuse and global in gray matter, and the changes occur rapidly, closely following the respiratory pattern. It is noteworthy that these BOLD changes showed very low variability across runs. fMRI studies measuring cerebral blood flow (instead of BOLD signal intensity) yield similar conclusions and show relatively small intersubject variability.

Research also demonstrates that this relatively nonspecific, respiratory-induced effect does not mask the specific, task-induced fMRI patterns. Using breath-holding challenge as a hypercapnic stimulus, the effects of photic stimulation on regional cerebral blood flow (rCBF) were examined under normal and hypercapnic conditions [personal communication Li & Kastrup, 155, 160]. Despite the significant change in baseline values, the rCBF increase during visual stimulation was very similar under both respiratory conditions. Together, these findings support the notion that within wide physiological variations, task-induced cerebral blood flow changes are independent of baseline rCBF values.

Research on a various forms of respiratory challenge, e.g., CO_2 inhalation, hyperventilation, breath-holding, etc., versus normal breathing have reported reproducible networks of forebrain and brainstem activation based on significant and specific changes in BOLD signal intensity. Furthermore, these patterns are discernible even with the considerable confounds of respiratory-induced variability of head and brainstem position, as well as wide variations in blood gas values. In contrast, the spontaneous breath-quiescence periods during the TM practice occur under relaxed, non-stressful conditions, with the onset, persistence and offset of spontaneous breath-quiescence not dependent upon volitional or intentional control or even awareness of the individual. Because of the restful state of the meditator, there is also minimal head movement artifact. **In conclusion, we anticipate that the potentially small, independent effects of respiratory-mediated BOLD signal changes will not significantly confound the data collected during spontaneous breath-quiescence substate of the TM technique.**

D.6.2.2 Effectsof cessation of mechanical respiratory activity. Intentional breath-holding will be used to clarify the impact of breath-quiescence on brain function and MRI signal intensity. These breath-holding periods will allow comparison of CO_2 variation and control for effects arising from cessation of mechanical respiratory activity. Because breath-quiescence occurs spontaneously during TM practice, the cycling protocol cannot be used requiring the recording of images during a "self-paced" protocol, in which no instructions are given and TM is uninterrupted. This non-cycling design will produce a 5 min time-series of scans that will have reoccurring periods of spontaneous breath-quiescence embedded in it. In addition, analytical approaches will be used that are capable of marking desired scans and comparing the variability of signal intensity in the time series. Event-related and state-related fMRI methodologies will be used to analyze the continuous sequence of scans [personal communication, Buckner and Braver, 2001][Buckner, 1998 #4780;Buckner, 1998 #4781;McCarthy, 1999 #5209;Schacter, 1997 #5391].

This confound should not affect the first phase (Aim 1), which investigates the initial de-excitation substate of meditation, because this substate occurs with little change in respiratory variables or alterations in blood gas levels [9, 22, 179]. The second phase (Aim 2) may be confounded by respiratory-induced BOLD effects, since we are imaging spontaneous breath quiescent (SBQ) periods. Research documents that nonspecific, respiratory-induced BOLD effects do not mask the detection of specific, task-induced fMRI

patterns [personal communication, Li, 2001; Glover, 2001; Moseley, 2001; Harper, 2001][Kastrup, 1999 #5077;Li, 1999 #5593;Li, 2000 #5155;Li, 2000 #5673;Kruger, 1999 #5665].

D.6.3. Methods.

The spontaneous breath-quiescent substate appears to be cessation of respiration or a slow continuous inhalation [22, 179]. During slow, protracted inhalation: (1) CO_2 will increase; (2) partial pressure in the lungs may vary; and (3) mechanical respiratory activity will essentially stop [157, 159, 207]. We will first investigate brain areas of significant signal change that arise from the consequences of breath-cessation itself (such as CO_2 and mechanical changes). These series of experiments will help determine the nature and magnitude of possible interactions between nonspecific, respiratory-induced and specific, meditation-induced changes in BOLD signal intensity. As stated previously, published studies suggest this interaction is independent and additive [personal communication, Glover, Mosely, Li, Harper; \Li, 2000 #5673;Kastrup, 1999 #5077;Kruger, 1999 #5665]. We expect to verify these findings and successfully differentiate BOLD signal responses that occur during breath-holding and spontaneous breath-quiescence periods.

The BOLD signal and physiological measures will be collected during four runs of 12 minutes duration each. Each 12 min run comprises three periods: 5 min uninterrupted meditation, 5 min structured breath-holding, and 2 mins non-task, eyes-closed (EC) control. The meditation period are free running with no interruptions from experimenters. During the meditation period we expect 3-5 SBQ periods. The breath-holding periods are structured by duplicating the previous SBQ pattern by voice command from experimenter, the onset and offset of IBH corresponding to SBQs time frame for each subject. The non-task control period will be determined from the outcome of experiment 1 (Aim 1), and either be passive-attending or mental-counting. The physiological measures will include respiration and transcutaneous CO_2 measurements. Four runs will take 48 minutes, or about 1 hr due to 30 rest periods between conditions. Therefore, each fMRI session will last about 90 minutes per subject.

D.6.4. Event-related fMRI analysis (Hypotheses 1-3).

Er-fMRI methodologies will be used to probe brain mechanisms during the onset of two conditions, during SBQ and IBH periods. The scans will be aligned relative to the onset of either SBQ or IBH during the four runs to permit signal averaging: 4 images before (12 secs) and 4 images after onset (12 secs). A TM meditator, selected in our screening protocol, may exhibit 25-30 spontaneous breath-quiescent periods in a 30-min TM session [9, 20-22]. We estimate 12-20 periods will occur in our four meditation periods.

Images from individual runs will first be normalized to correct for the range of intra- and inter-subject signal intensity and temporal drift [171]. Specifically, normalization will involve: (1) scaling of signal intensity to a fixed value of 1000; (2) linear slope removal in a voxel-by-voxel basis; (3) spatial filtering with a one-voxel radius Hanning filter, and; (4) removal of the mean signal intensity on a voxel-by-voxel basis. The normalized fMRI images will then be aligned relative to the onset either SBQ or IBH periods. These images will be averaged within each subject. The mean image for each subject will be transformed into stereotaxic atlas space [208] using the highest point of the mid-sagittal plane and the anterior and posterior commissures. The atlas-transformed matrices will then be averaged across subjects.

Statistical parameter maps will be constructed using sets of pre-constructed hemodynamic curves. Cohen's hemodynamic model, often used in fMRI experimental analysis, was derived from stimulation of the visual cortex [170]. Hence, there is no reason to suspect it is the best response function to apply to this task (meditation) or to other brain areas (subcortical nuclei). Therefore, new response models will be constructed by systematically varying, initially, the onset delay (lags) of Cohen's standard hemodynamic response model. Other parameters besides onset could also be varied, e.g., shape of curve. Sequential application of each model will display the inherent temporal and spatial dynamics of the hemodynamic response to the onset of the spontaneous breath-quiescent substate. Each model will generate a different map of the brain dynamics. For example, short versus mid or long lags could be reasonably expected to produce different anatomical patterns [171]. On the other hand, the brain pattern may remain similar, but the signal intensity of each brain area may vary. Models derived from both conditions can be compared to determine statistical significance of the two brain states. Specifically, we will use MANOVA to compare onset, latency and peak signal intensity for different ROIs for the two conditions. We expect, in general, that the statistical parameter maps for intentional breath-holding will depict a diffuse, non-localized distribution of activation in contrast to localized patterns of activation during spontaneous breath-quiescence. Hypothesis 1 & 2 will use a correlational analysis to test association between er-fMRI BOLD signal intensity and blood gas levels.

D.6.4.1 Blood Gases and IBH. O_2 and CO_2 levels will be correlated with er-fMRI BOLD signal intensity during the 6 scans (18 s) preceding and the 4 scans (12 s) following the onset of IBH. Data will be analyzed with a Pearson correlation to help distinguish blood gas-dependent vs. neural-dependent BOLD changes.

- We expect significant correlations between CO_2, but not O_2, with BOLD signal during IBH.

D.6.4.2. Blood Gases and SBQ.O_2 and CO_2 levels will be correlated with er-fMRI BOLD signal intensity during the 6 scans (18 s) preceding and the 4 scans (12 s) following the onset of spontaneous breath-quiescence. Data will be analyzed with a Pearson correlation help distinguish blood gas-dependent versus neural-dependent BOLD changes.

- We expect minor blood gas changes and hence, few significant correlations between CO_2, with BOLD signal during spontaneous breath-quiescence.

D.6.4.3. Neuroimages during SBQ and IBH. Er-fMRI will be compared between IBH and SBQ periods, using a repeated measures MANOVA.

- We expect main effects for brain areas. Animal hypercapnia [209] and human breath-holding [157, 203, 210, 211] studies indicate that hypercapnic conditions are associated with global increases in most cortical and subcortical grey matter blood flow. Thus, we expect region-independent, nonspecific activation in all areas during IBH. In contrast, we expect region-dependent, specific activation or deactivation of BOLD signal intensity during SBQ.
- We expect main effects for the repeated measures, indicating significant differences in signal intensity across time.
- We expect no significant interactions.

D.6.5. State-related fMRI analysis (Hypotheses 4-5).

Sr-fMRI methodologies will be used to probe brain mechanisms during SBQ, IBH, and control periods. In the previous three analyses, we identified brain areas that displayed significant time-locked relation to the onset of both IBH and SBQ. A complementary approach to identification of brainstate changes is the use of state-related methodology. This method divides the time-series into condition-specific bins for comparison. Scans collected in Expt. 2 will be categorized into six bins: before and during either IBH, SBQ or equal-length periods during eyes-close (EC) control. Scans assigned to each bin will be compared by multiple linear regression, correcting for differences in blood gas levels across the three conditions.

D.6.5.1. Sequence of Analysis. First, we will create a dummy time-series of 1, or 2's that correspond to the scans before and during three conditions: IBH, SBQ or EC. The dummy time-series then will be convolved with the hemodynamic response model using the Cohen Model. This will yield the dummy independent variable that will be entered into the multiple linear regression analysis along with O_2 and CO_2 data. The scans for each of the periods will be dependent variables in the analysis. We will examine the resulting statistical parameter maps for clusters of pixels displaying significant fluctuations in signal intensity. The *Z*-statistic of the activated clusters that meet our criteria (D.2.3.) will be entered as variates in a repeated-measures ANOVA, with brain area as the factor and the period as the repeated measures.

D.6.5.2. Comparisonbetween conditions: SBQ, IBH and EC. Condition differences will be assessed with two-way repeated measures ANOVA with brain areas and condition as factors, and the two periods (before and during the conditions) as the repeated measures. Individual comparison will be conducted if there are significant main effects.

- We expect no main effects for brain areas, indicating highly variable activation across brain areas yielding no consistent relations.
- We expect main effects for condition (SBQ, IBH, EC), indicating different brain mechanisms are active during each condition. For example, during IBH we expect higher levels of task effort and motor system activation, and possibly higher CO_2 levels to yield the predicted main effect.
- We expect main effects for the repeated measure (before and during). The 'before' periods may be somewhat similar, while the 'during' periods may be significantly different.
- We expect significant interactions, indicating differential involvement of some brain areas during the three conditions. For instance, the cerebral cortex may exhibit lower BOLD signal in both 'before' periods. However, the cortex is expected to be activated during IBH, while remaining low or reduced during SBQ.

D.6.6. Outcome. This experiment will help identify:

(1) Neural mechanisms specific to the generation and maintenance of IBH, and the effects of hypercapnia and loss of mechanical respiratory activity on BOLD signal intensity.
(2) Neural mechanisms specific to SBQ periods, as compared to a variety of brainstates, including, other meditation periods, IBH, and EC.

D.7. Conclusion of Research Design and Methods.

These data should help elucidate the spatiotemporal structure of neurophysiological processes during the practice of TM. Previous EEG and autonomic research have provided a rough map of the possible brain mechanisms underlying distinct substates of meditation [7-9, 22]. Data obtained from this R21 neuroimaging research should provide a more reliable and accurate model of brain mechanisms underlying TM practice. The proposed research will provide: (1) a tested fMRI protocol for imaging meditation experience; (2) a determination of signal sources during two principal substates of TM practice; and (3) key experimental protocol and analysis issues to yield successful comparative studies of meditation. The systematic substate characterization resulting from this grant will enable researchers to generalize the research methodology and mechanisms to the investigation of other meditation techniques, and thereby, facilitate relatively rapid progress in employing the new field of neuroimaging to examine brain dynamics of meditation. Progress in understanding brain dynamics of meditation and other CAM techniques will depend upon such careful substate research.

G. LITERATURE CITED

1. **Eisenberg, D.M., et al.,** ***Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey.*** **Jama, 1998. 280(18): p. 1569-75.**
2. **Eisenberg, D., et al.,** ***Unconventional medicine in the United States: Prevalence, costs, and patterns of use.*** **The New England Journal of Medicine, 1993. 328(4): p. 246-252.**
3. **Roth, R.,** ***The Transcendental Meditation Program.*** **1994, New York: Primus Publishing, Inc.**
4. **Chalmers, R., et al., eds.** ***Scientific Research on the Transcendental Meditation program: Collected Papers (Vol. 2-4).*** **1990, MVU Press: Vlodrop, The Netherlands.**
5. **Orme-Johnson, D.W. and J. Farrow, eds.** ***Scientific Research on the Transcendental Meditation program: Collected Papers (Vol. 1).*** **1977, MERU Press: Rheinweiler, West Germany.**
6. **Wallace, R.K., D.W. Orme-Johnson, and M.C. Dillbeck, eds.** ***Scientific Research on the Transcendental Meditation Program: Collected Papers, Vol. 5.*** **1990, MIU Press: Fairfield, Iowa.**
7. **Arenander, A.T.,** ***Brain state and attentional mechanisms in the transition to a de-excited state of consciousness: A neuro-psychological model of transcending.*** **Soc. Neurosci. Abst., 1986. 16: p. 1446.**
8. **Arenander, A.T.** ***Global Neural Ground State: Coherent brain mechanisms associated with Transcendental Consciousness.*** **in** ***Toward a Science of Consciousness.*** **1996. Tucson, AZ.**
9. **Travis, F. and R.K. Wallace,** ***Autonomic and EEG patterns during eyes-closed rest and transcendental meditation (TM) practice: the basis for a neural model of TM practice.*** **Conscious Cogn, 1999. 8(3): p. 302-18.**
10. **Travis, F. and C. Pearson,** ***Pure consciousness: distinct phenomenological and physiological correlates of "consciousness itself".*** **Int J Neurosci, 2000. 100(1-4): p. 77-89.**
11. **Wallace, R.K.,** ***The Physiological Effects of Trancendental Meditation: A Proposed Fourth Major State of Consciousness,*** **in** ***Scientific Research on the Transcendental Meditation Program Collected Papers,*** **F.F. D. Orme-Johnson, Editor. 1970, MERU: Livingston New York. p. 43-78.**
12. **Travis, F., et al.,** ***Patterns of EEG coherence, power, and contingent negative variation characterize the integration of transcendental and waking states.*** **Biol Psychology, 2002. In Press: p. 1-27.**
13. **NCCAM,** ***NCCAM Five Year Strategic Plan 2001-2005.*** **2000, DC: National Center for Complimentary and Alternative Medicine.**
14. **Cohen, M.S.,** ***Rapid MRI and Functional Applications,*** **in** ***Brain Mapping: the Methods,*** **A.W. Toga and J.C. Mazziotta, Editors. 1996, Academic Press: New York.**
15. **Astin, J.A.,** ***Why patients use alternative medicine: results of a national study.*** **Journal of the American Medical Association, 1998. 279: p. 1548-1553.**
16. **Burkman, L. and L. Breslow,** ***Book and Ways of Living: The Alameida County Study.*** **1983, Cambridge, MA: Oxford University Press.**
17. **Weinstein, M.D. and W.B. Stason,** ***Hypertension: A Policy Perspective.*** **1976, Cambridge, MA: Harvard University Press.**
18. **Campion, E.W.,** ***Why unconventional medicine?*** **New England Journal of Medicine, 1993. 328: p. 282-283.**
19. **Orme-Johnson, D. and K. Walton,** ***All approaches to preventing or reversing effects of stress are not the same.*** **American Journal of Health Promotion, 1998. 12(5): p. 297-299.**
20. **Farrow, J. and J. Hebert,** ***Breath suspension during the Transcendental Meditation technique.*** **Psychosomatic Medicine, 1982. 44(2): p. 133-153.**
21. **Badawi, K., et al.,** ***Electrophysiologic characteristics of respiratory suspension periods occurring during the practice of the Transcendental Meditation Program.*** **Psychosom Med, 1984. 46(3): p. 267-76.**
22. **Travis, F. and R.K. Wallace,** ***Autonomic patterns during respiratory suspensions: possible markers of Transcendental Consciousness.*** **Psychophysiology, 1997. 34(1): p. 39-46.**
23. **Maharishi,** ***Science of Being the Art of Living.*** **1963, New York: New American Library Inc.**
24. ***Health United States, 1988. DHHS Pub. No. (PHS) 89-1232 Public Health Service,*** **ed. N.C.f.H. Statistics. 1989, Washington, DC: U.S.: Goverment Printing Office.**
25. **Walton, K.G., et al.,** ***Stress reduction and preventing hypertension: preliminary support for a psychoneuroendocrine mechanism.*** **Journal of Alternative and Complementary Medicine, 1995. 1(3): p. 263-283.**
26. **MacLean, C., et al.,** ***Effects of the Transcendental Meditation program on adaptive mechanisms: changes in hormone levels and responses to stress after 4 months of practice.*** **Psychoendrocrinology, 1996. 22(4): p. 277-295.**
27. **MacLean, C.R.K., et al.,** ***Altered responses of cortisol, GH, TSH and testosterone to acute stress after four month's practice of Transcendental Meditation (TM).*** **Annals of the New York Academy of Sciences, 1994. 746: p. 381-384.**

28. **Levitsky, D.K., et al.,** ***Reversal of neuroendocrine effects of chronic stress by the Transcendental Meditation technique.*** **Society for Neuroscience Abstracts, 1995. 21(2): p. 1389.**
29. **Albright, G.L., Andreassi, J. L., Brockwell, A. L.,** ***Effects of stress management on blood pressure and other cardiovascular variables.*** **International Journal of Psychophysiology, 1991. 11: p. 213-217.**
30. **Alexander, C.N., et al.,** ***Effects of the Transcendental Meditation program on stress reduction, health, and employee development: A prospective study in two occupational settings.*** **Anxiety, Stress and Coping: An International Journal, 1993. 6: p. 245-262.**
31. **Alexander, C.N., et al.,** ***A randomized controlled trial of stress reduction on cardiovascular and all-cause mortality in the elderly: Results of 8 and 15 year follow-ups.*** **Circulation (abstract), 1996. 93(3): p. P19.**
32. **Bairey, C.N., D.S. Krantz, and A. Rozanski,** ***Mental stress as an acute trigger of ischemic left ventricular dysfunction and blood pressure elevation in coronary artery disease.*** **American Journal of Cardiology, 1990. 66(16): p. 28G-31G.**
33. **Lindvall, K., et al.,** ***Stress-induced hanges in blood pressure and left ventricular function in mild hypertension.*** **Clinical Cardiology, 1991. 14(2): p. 125-132.**
34. **Wenneberg, S.R., et al.,** ***A controlled study of the effects of the Transcendental Meditation program on cardiovascular reactivity and ambulatory blood pressure.*** **Int J Neurosci, 1997. 89(1-2): p. 15-28.**
35. **Schneider, R.H., et al.,** ***A randomized controlled trial of stress reduction for hypertension in older Africa Americans.*** **Hypertension, 1995. 26: p. 820-827.**
36. **Herron, R.E., et al.,** ***Cost-effective hypertension management: Comparison of drug therapies with an alternative program.*** **The American Journal of Managed Care, 1996. 2(4): p. 427-437.**
37. **Castillo-Richmond, A., et al.,** ***Effects of stress reduction on carotid atherosclerosis in hypertensive African Americans.*** **Stroke, 2000. 31(3): p. 568-73.**
38. **Cooper, M.J. and M.M. Aygen,** ***Effect of Transcendental Meditation on serum cholesterol and blood pressure. Harefuah,*** **the Journal of the Israel Medical Association, 1987. 95(1): p. 1-2.**
39. **Calderon, R., Jr., et al.,** ***Stress, stress reduction and hypercholesterolemia in African Americans: a review.*** **Ethn Dis, 1999. 9(3): p. 451-62.**
40. **Royer, A.,** ***The role of the Transcendental Meditation technique in promoting smoking cessation: A longitudinal study.*** **Alcoholism Treatment Quarterly, 1994. 11.**
41. **Royer-Bounouar, A.,** ***The Transcendental Meditation technique: a new direction for smoking cessation programs.*** **1989, Maharishi International University.**
42. **Gelderloos, P., et al.,** ***The effectiveness of the Transcendental Meditation program in preventing and treating substance abuse: A review.*** **International Journal of the Addictions, 1991. 26: p. 297-325.**
43. **Alexander, C.N., P. Robinson, and M. Rainforth,** ***Treatment and prevention of drug addiction through Transcendental Meditation: An overview and statistical meta-analysis.*** **Alcoholism Treatment Quarterly, 1993: p. 11-84.**
44. **Alexander, C.N., P. Robinson, and M. Rainforth,** ***Treating alcohol, nicotine and drug abuse through Transcendental Meditation: A review and statistical meta-analysis.*** **Alcoholism Treatment Quarterly, 1994.**
45. **Clayborne, B., et al.** ***Effects of stress reduction on anger and cardiovascular reactivity in hypertensive African Americans: A randomized, controlled trial of Transcendental Meditation and progressive relaxation.*** **in** ***12th International Conference on Hypertension in Blacks.*** **1997. London.**
46. **Dillbeck, M.C.,** ***The effect of the Transcendental Meditation technique on anxiety level.*** **J Clin Psychol, 1977. 33(4): p. 1076-8.**
47. **Dillbeck, M.C., M.B. Clayborne, and S.L. Dillbeck.** ***Effects of the Transcendental Meditation program with low-income inner-city children.*** **in** ***Paper presented at 98th Annual Convention of the American Psychological Association.*** **1990. Boston, Massachusetts.**
48. **Alexander, C.N., et al.** ***Effects of Transcendental Meditation on psychological risk factors, cardiovascular and all-cause mortality: a review of meta-analyses and controlled clinical trials.*** **in** ***Tenth Conference of the European Health Psychology Society.*** **1996. Dublin, Ireland.**
49. **Nader, T., et al.,** ***Improvements in chronic diseases with a comprehensive natural medicine approach: A case series.*** **submitted.**
50. **Orme-Johnson, D.W.,** ***Medical care utilization and the Transcendental Meditation program.*** **Psychosomatic Medicine, 1987. 49: p. 493–507.**
51. **Alexander, C.N., et al.,** ***Effects of Transcendental Meditation compared to other methods of relaxation and meditation in reducing risk factors, morbidity and mortality.*** **Homeostasis, 1994. 35(3-4): p. 243-264.**

52. **Herron, R.E., et al.,** ***The impact of the Transcendental Meditation program on government payments to physicians in Quebec.*** **American Journal of Health Promotion, 1996. 10(3): p. 208-216.**
53. **Orme-Johnson, D.W. and R.E. Herron,** ***An innovative approach to reducing medical care utilization and expenditures.*** **The American Journal of Managed Care, 1997. 3(1): p. 135-144.**
54. **Orme-Johnson, D.W. and R.M. Herron,** ***Medical care utilization, Transcendental Meditation, and Maharishi Ayur-Ved.*** **American Journal of Health Promotion, in review.**
55. **Smith, J.C.,** ***Meditation, biofeedback, and the relaxation controversy: A cognitive-behavioral perspective.*** **American Psychologist, 1986. 41: p. 1007-1009.**
56. **Smith, J.C., et al.,** ***Relaxation: Mapping an Uncharted World.*** **Biofeedback and Self-Regulation, 1996. 21(No. 1): p. 63-90.**
57. **Lehrer, P.M., et al.,** ***Stress management techniques: Are they all equivlalent, or do they have specific effects?*** **Biofeedback and Self-Regulation, 1994. 19: p. 353-401.**
58. **Davidson, R.J. and G.E. Schwartz,** ***Psychobiology of relaxation and related states.*** **Behavior modification and control of physiological activity., ed. D.E. Mostofsky. 1976, Englewood Cliffs, NJ: Prentice-Hall.**
59. **Schwartz, G.E., R.J. Davidson, and D.T. Goleman,** ***Patterning of cognitive and somatic processes in the self-regulation of anxiety: Effects of meditation versus exercise.*** **Psychosomatic Medicine, 1978. 40: p. 321-328.**
60. **Eppley, K., Abrams, A., Shear, J.** ***The Effects of Meditation and Relaxation Techniques on Trait Anxiety, a Meta-Analysis.*** **in** ***Convention of the American Psychological Association.*** **1984. Toronto, Canada.**
61. **Eppley, K., A.I. Abrams, and J. Shear,** ***Differential effects of relaxation techniques on trait anxiety: A meta-analysis.*** **Journal of Clinical Psychology, 1989. 45(6): p. 957–974.**
62. **Alexander, C.N., M.Y. Rainforth, and P. Gelderloos,** ***Transcendental Meditation, Self-Actualization and Psychological Health: A Conceptual Overview and Statistical Meta-Analysis.*** **Journal of Social Behavior and Personality, 1991. 6(5): p. 189-247.**
63. **Barnes, V., et al.,** ***Stress, stress reduction, and hypertension in African Americans: an updated review.*** **J Natl Med Assoc, 1997. 89(7): p. 464-76.**
64. **Dillbeck, M.C. and D.W. Orme-Johnson,** ***Physiological differences between Transcendental Meditation and rest.*** **American Psychologist, 1987. 42: p. 879–881.**
65. **Andresen, J. and R.K.C. Forman, eds.** ***Cognitive Models and Spiritual Maps.*** **Vol. 7 (11-12). 2000, Journal of Consciousness Studies. 1-287.**
66. **Arenander, A.T.,** ***The Transcending Brain: Neurocognitive mechanisms underlying a proposed 4th state of consciousness.*** **, in** ***Seminars in the Science of Creative Intelligence.*** **1975: Montery, CA. p. 1-30.**
67. **Arenander, A.T., et al.,**

Analysis of EEG coherence during spontaneous respiratory suspension. **Soc. Neuroscience Absract, 1985. 15(867).**

68. **Travis, F.,** ***The Transcendental Meditation technique and creativity: A longitudinal study of Cornell University undergraduates.*** **Journal of Creative Behavior, 1979b. 13: p. 169-180.**
69. **Travis, F.T.,** ***The junction point model: A field model of waking, sleeping, and dreaming, relating to dream witnessing, the waking/sleeping transition, and Transcendental Meditation in terms of a common psychophysiological state.*** **Dreaming, 1994. 4(No. 2): p. 91-104.**
70. **Ferguson, P.C.,** ***An integratiave meta-analysis of psychological studies investigating the treatment outcomes of meditation techniques.*** **1980, University of Colorado.**
71. **Kuchera, M.,** ***The effectiveness of meditation techniques to reduce blood pressure levels: A meta-analysis.*** **Dissertation Abstracts International, 1987. 47(11-B): p. 4639.**
72. **Ferguson, P.,** ***An integrative meta-analysis of psychosocial studies integrating the treatment outcomes of meditation techniques.*** **1981, School of Education, University of Colorado, Boulder.**
73. **Newberg, A., et al.,** ***The measurement of regional cerebral blood flow during the complex cognitive task of meditation: a preliminary SPECT study.*** **Psychiatry Res, 2001. 106(2): p. 113-22.**
74. **Kleitman, N.,** ***The basic rest--activity cycle and physiological correlates of dreaming.*** **Exp Neurol, 1967: p. Suppl 4:2-4.**
75. **Tononi, G. and C. Cirelli,** ***Modulation of Brain Gene Expression during Sleep and Wakefulness. A Review of Recent Findings.*** **Neuropsychopharmacology, 2001. 25(5 Suppl 1): p. S28-35.**
76. **Benhamou, I.,** ***Sleep disorders of early childhood: a review.*** **Isr J Psychiatry Relat Sci, 2000. 37(3): p. 190-6.**
77. **Goh, V.H., T.Y. Tong, and L.K. Lee,** ***Sleep/wake cycle and circadian disturbances in shift work: strategies for their management--a review.*** **Ann Acad Med Singapore, 2000. 29(1): p. 90-6.**
78. **Waite, P.D.,** ***Obstructive sleep apnea: a review of the pathophysiology and surgical management.*** **Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 1998. 85(4): p. 352-61.**

79. **Robert, C., C. Guilpin, and A. Limoge, *Review of neural network applications in sleep research.* J Neurosci Methods, 1998. 79(2): p. 187-93.**
80. **Benca, R.M. and J. Quintas, *Sleep and host defenses: a review.* Sleep, 1997. 20(11): p. 1027-37.**
81. **Anders, T.F. and L.A. Eiben, *Pediatric sleep disorders: a review of the past 10 years.* J Am Acad Child Adolesc Psychiatry, 1997. 36(1): p. 9-20.**
82. **Coy, T.V., et al., *Sleep apnoea and sympathetic nervous system activity: a review.* J Sleep Res, 1996. 5(1): p. 42-50.**
83. **Ohta, T., *Circadian rhythm sleep disorders: a brief review with special reference to long-term follow-up.* Nagoya J Med Sci, 1995. 58(3-4): p. 83-93.**
84. **Kanellakos, D.P., *The physiology of the evolving man*. Scientific Research on the Transcendental Meditation Program. Collected Papers, Volume I., ed. D.W.F. Orme-Johnson, J.T. Vol. 1. 1969: Maharishi European Research University Press. 727.**
85. **Glueck, B.C. and C.F. Stroebel, *Biofeedback and meditation in the treatment of psychiatric illnesses.* Comprehensive Psychiatry, 1985. 16: p. 303-321.**
86. **Elias, A.N., S. Guich, and A.F. Wilson, *Ketosis with enhanced GABAergic tone promotes physiological changes in transcendental meditation.* Med Hypotheses, 2000. 54(4): p. 660-2.**
87. **Elias, A.N. and A.F. Wilson, *Serum hormonal concentrations following transcendental meditation--potential role of gamma aminobutyric acid.* Med Hypotheses, 1995. 44(4): p. 287-91.**
88. **Zamarra, J.W., et al., *Usefulness of the Transcendental Meditation program in the treatment of patients with coronary artery disease.* American Journal of Cardiology, 1996. 78: p. 77-80.**
89. **Kondwani, K., et al. *Effects of lifestyle modification on left ventricular mass and diastolic function in hyptertensive African Americans: A trial of the Transcendental Meditation Technique and a diet and exercise program (abstract)*. in *Twelfth International conference on Hypertension in Blacks*. 1997. London.**
90. **Schneider, R.H., et al., *Meta-analysis of randomized controlled trials of stress reduction and the Transcendental Meditation program on mortality.* Journal of the American Medical Association, (submitted).**
91. **Schneider, R.H., et al., *Disease prevention and health promotion in the aging: a review of modern and traditional Maharishi Ayur-veda approaches.* The Journal of Alternative and Complimentary Medicine, in press. 1(4).**
92. **Barnes, V.A., et al., *Effects of stress reduction on mortality in older African Americans with hypertension—five year follow-up.* in review.**
93. **Barnes, V.A., et al. *Randomized trial of stress reduction in older African American hypertensives: 5 year follow-up on all-cause and CVD mortality*. in *Presented at the Eleventh Interdisciplinary Conference, International Society on Hypertension in Blacks*. July, 1996. New Orleans.**
94. **Castillo-Richmond, A., et al., *A Randomized Controlled Trial of Stress Reduction and Carotid Atherosclerosis in Hypertensive African Americans.* submitted.**
95. **Gozal, D., et al., *Localization of putative neural respiratory regions in the human by functional magnetic resonance imaging.* J Appl Physiol, 1994. 76(5): p. 2076-83.**
96. **Harper, R.M., et al., *Regional brain activation in humans during respiratory and blood pressure challenges.* Clin Exp Pharmacol Physiol, 1998. 25(6): p. 483-6.**
97. **Harper, R.M., M.A. Woo, and J.R. Alger, *Visualization of sleep influences on cerebellar and brainstem cardiac and respiratory control mechanisms [In Process Citation].* Brain Res Bull, 2000. 53(1): p. 125-31.**
98. **Negoescu, R., J.E. Skinner, and S. Wolf, *Forebrain regulation of cardiac function spectral and dimensional analysis of RR and QT intervals.* Integr Physiol Behav Sci, 1993. 28(4): p. 331-42.**
99. **Skinner, J.E., *Neurocardiology. Brain mechanisms underlying fatal cardiac arrhythmias.* Neurol Clin, 1993. 11(2): p. 325-51.**
100. **Skinner, J.E., C.M. Pratt, and T. Vybiral, *A reduction in the correlation dimension of heartbeat intervals precedes imminent ventricular fibrillation in human subjects.* Am Heart J, 1993. 125(3): p. 731-43.**
101. **Skinner, J.E., et al., *Application of chaos theory to a model biological system: evidence of self-organization in the intrinsic cardiac nervous system.* Integr Physiol Behav Sci, 1996. 31(2): p. 122-46.**
102. **Alexander, C.N., et al., *Rehabiliation From WIthin: Reducing Crime and Violence through the Transcendental Meditation program*. In press: Journal of Offender Rehabilitation.**
103. **Garbarino, J., *Lost Boys: Why are sons turn violent and how we can save them*. 1999, New York: Anchor Books.**
104. **Garbarino, J., *Violent children: where do we point the finger of blame?* Arch Pediatr Adolesc Med, 2001. 155(1): p. 13-4.**
105. **Niehoff, D., *The Biology of Violence: How Understanding the Brain, Behavior, and Environment Can Break the Vicious Circle of Aggression*. 1999, New York: The Free Press, Simon & Schuster.**

106. **Raine, A., et al., *Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers.* Behav Sci Law, 1998. 16(3): p. 319-32.**
107. **Volavka, J., *The neurobiology of violence: an update.* J Neuropsychiatry Clin Neurosci, 1999. 11(3): p. 307-14.**
108. **Bush, G., et al., *Anterior cingulate cortex dysfunction in attention- deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop.* Biol Psychiatry, 1999. 45(12): p. 1542-52.**
109. **Rubia, K., et al., *Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI.* Neurosci Biobehav Rev, 2000. 24(1): p. 13-9.**
110. **Vaidya, C.J., et al., *Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study.* Proc Natl Acad Sci U S A, 1998. 95(24): p. 14494-9.**
111. **Cabeza, R. and L. Nyberg, *Imaging cognition II: An empirical review of 275 PET and fMRI studies.* J Cogn Neurosci, 2000. 12(1): p. 1-47.**
112. **DeYoe, E.A., et al., *Functional magnetic resonance imaging (FMRI) of the human brain.* J Neurosci Methods, 1994. 54(2): p. 171-87.**
113. **Farah, M.J. and G.K. Aguirre, *Imaging visual recognition: PET and fMRI studies of the functional anatomy of human visual recognition.* Trends Cogn Sci, 1999. 3(5): p. 179-186.**
114. **Savoy, R., *Magnetic Resonance Imaging (MRI).* 2nd Edition ed. Encyclopedia of Neuroscience, ed. G.a.S. Adelman, BH (Eds). 1999: Elsevier.**
115. **Logothetis, N.K., et al., *Neurophysiological investigation of the basis of the fMRI signal.* Nature, 2001. 412(6843): p. 150-7.**
116. **Raichle, M.E., *Cognitive neuroscience. Bold insights.* Nature, 2001. 412(6843): p. 128-30.**
117. **Cho, Z.H., et al., *New findings of the correlation between acupoints and corresponding brain cortices using functional MRI.* Proc Natl Acad Sci U S A, 1998. 95(5): p. 2670-3.**
118. **Wu, M.T., et al., *Central nervous pathway for acupuncture stimulation: localization of processing with functional MR imaging of the brain--preliminary experience.* Radiology, 1999. 212(1): p. 133-41.**
119. **Hui, K.K., et al., *Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in normal subjects.* Hum Brain Mapp, 2000. 9(1): p. 13-25.**
120. **Yoshida, T., et al., *Non-invasive measurement of brain activity using functional MRI: toward the study of brain response to acupuncture stimulation.* Am J Chin Med, 1995. 23(3-4): p. 319-25.**
121. **Maquet, P., et al., *Functional neuroanatomy of hypnotic state.* Biol Psychiatry, 1999. 45(3): p. 327-33.**
122. **Buchanan, T.W., et al., *Recognition of emotional prosody and verbal components of spoken language: an fMRI study.* Brain Res Cogn Brain Res, 2000. 9(3): p. 227-38.**
123. **Gallagher, H.L., et al., *Reading the mind in cartoons and stories: an fMRI study of 'theory of mind' in verbal and nonverbal tasks.* Neuropsychologia, 2000. 38(1): p. 11-21.**
124. **Henson, R.N., N. Burgess, and C.D. Frith, *Recoding, storage, rehearsal and grouping in verbal short-term memory: an fMRI study.* Neuropsychologia, 2000. 38(4): p. 426-40.**
125. **Iidaka, T., et al., *Functional asymmetry of human prefrontal cortex in verbal and non- verbal episodic memory as revealed by fMRI.* Brain Res Cogn Brain Res, 2000. 9(1): p. 73-83.**
126. **Chee, M.W., et al., *Auditory and visual word processing studied with fMRI.* Hum Brain Mapp, 1999. 7(1): p. 15-28.**
127. **Chen, W., et al., *Mapping of lateral geniculate nucleus activation during visual stimulation in human brain using fMRI [published erratum appears in Magn Reson Med 1998 Mar;39(3):following 505].* Magn Reson Med, 1998. 39(1): p. 89-96.**
128. **Clark, V.P., et al., *Responses to rare visual target and distractor stimuli using event- related fMRI.* J Neurophysiol, 2000. 83(5): p. 3133-9.**
129. **Paradis, A.L., et al., *Visual perception of motion and 3-D structure from motion: an fMRI study.* Cereb Cortex, 2000. 10(8): p. 772-83.**
130. **Poldrack, R.A., et al., *The neural basis of visual skill learning: an fMRI study of mirror reading.* Cereb Cortex, 1998. 8(1): p. 1-10.**
131. **Waldvogel, D., et al., *The variability of serial fMRI data: correlation between a visual and a motor task.[In Process Citation].* Neuroreport, 2000. 11(17): p. 3843-7.**
132. **Lotze, M., et al., *Activation of cortical and cerebellar motor areas during executed and imagined hand movements: an fMRI study.* J Cogn Neurosci, 1999. 11(5): p. 491-501.**
133. **Hofle, N., et al., *Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans.* J Neurosci, 1997. 17(12): p. 4800-8.**
134. **Fiset, P., et al., *Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study.* J Neurosci, 1999. 19(13): p. 5506-13.**

135. **Paus, T., *Functional anatomy of arousal and attention systems in the human brain.* Prog Brain Res, 2000. 126: p. 65-77.**
136. **Bonhomme, V., et al., *Propofol anesthesia and cerebral blood flow changes elicited by vibrotactile stimulation: a positron emission tomography study.* J Neurophysiol, 2001. 85(3): p. 1299-308.**
137. **Gusnard, D.A., et al., *Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function.* Proc Natl Acad Sci U S A, 2001. 98(7): p. 4259-64.**
138. **Raichle, M.E., et al., *A default mode of brain function.* Proc Natl Acad Sci U S A, 2001. 98(2): p. 676-82.**
139. **Mintun, M.A., et al., *Blood flow and oxygen delivery to human brain during functional activity: theoretical modeling and experimental data.* Proc Natl Acad Sci U S A, 2001. 98(12): p. 6859-64.**
140. **Gusnard, D.A. and M.E. Raichle, *Searching for a baseline: functional imaging and the resting human brain.* Nat Rev Neurosci, 2001. 2(10): p. 685-94.**
141. **Raichle, M.E. and D.A. Gusnard, *Appraising the brain's energy budget.* Proc Natl Acad Sci U S A, 2002. 99(16): p. 10237-9.**
142. **Herzog, H., et al., *Changed pattern of regional glucose metabolism during yoga meditative relaxation.* Neuropsychobiology, 1990. 23(4): p. 182-7.**
143. **Lazar, S.W., et al., *Functional brain mapping of the relaxation response and meditation.* Neuroreport, 2000. 11(7): p. 1581-5.**
144. **Lou, H.C., et al., *A 15O-H2O PET study of meditation and the resting state of normal consciousness.* Hum Brain Mapp, 1999. 7(2): p. 98-105.**
145. **Lehmann, D., et al., *Theta bursts of high amplitude and vigilance level during transcendental meditation.* Sleep Research Abstracts, 1976. 5: p. 137.**
146. **Levine, P.H., Russell, J. H., Haynes, C.T.,Strobel, U., *EEG Coherence During the Transcendental Meditation Technique*, in *Scientific Research on the Transcendental Meditation Program :Collected Papers*, D. Orme-Johnson, Farrow, J., Editor. 1975, MERU: Livingston Mannor NY. p. 187-207.**
147. **Haynes, C.T., et al., *Correlations of EEG coherence, creativity, H-reflex recovery, and the experience of transcendental consciousness.* Scientific Research on Maharishi's Transcendental Meditation and TM-Sidhi Program, 1976. 1: p. 48-54.**
148. **Gaylord, C., D. Orme-Johnson, and F. Travis, *The effects of the Transcendental Meditation technique and progressive muscle relaxation on EEG coherence, stress reactivity, and mental health in black adults.* International Journal of Neuroscience, 1989. 46: p. 77-86.**
149. **Travis, F. and S. Miskow, *P300 latency and amplitute during eye-closed rest and Transcendental Meditation practice.* Psychophsiology, 1994. 31: p. S67 (Abstract).**
150. **Travis, F., *Cortical and cognitive development in 4th, 8th and 12th grade students. The contribution of speed of processing and executive functioning to cognitive development.* Biol Psychol, 1998. 48(1): p. 37-56.**
151. **Travis, F. and J.J. Tecce, *Effects of distracting stimuli on CNV amplitude and reaction time.* Int J Psychophysiol, 1998. 31(1): p. 45-50.**
152. **Travis, F., *A second linked-reference issue: possible biasing of power and coherence spectra.* Int J Neurosci, 1994. 75(1-2): p. 111-7.**
153. **Mason, L.I., et al., *Electrophysiological correlates of higher states of consciousness during sleep in long-term practitioners of the Transcendental Meditation program.* Sleep, 1997. 20(2): p. 102-10.**
154. **Travis, F., J.J. Tecce, and J. Guttman, *Cortical plasticity, contingent negative variation, and transcendent experiences during practice of the Transcendental Meditation technique.* Biological Psychiatry, 2000. 55: p. 41-55.**
155. **Kastrup, A., et al., *Relationship between cerebral blood flow changes during visual stimulation and baseline flow levels investigated with functional MRI.* Neuroreport, 1999. 10(8): p. 1751-6.**
156. **Li, T.Q., M.E. Moseley, and G. Glover, *A FAIR study of motor cortex activation under normo- and hypercapnia induced by breath challenge.* Neuroimage, 1999. 10(5): p. 562-9.**
157. **Li, T.Q., et al., *Functional MRI of human brain during Breath-Holding by BOLD and FAIR techniques.* Neuroimage, 1999. 9(2): p. 243-9.**
158. **Glover, G.H., T.Q. Li, and D. Ress, *Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR.* Magn Reson Med, 2000. 44(1): p. 162-7.**
159. **Li, T.Q., et al., *Assessment of hemodynamic response during focal neural activity in human using bolus tracking, arterial spin labeling and BOLD techniques [In Process Citation].* Neuroimage, 2000. 12(4): p. 442-51.**
160. **Li, T.Q., et al., *Changes in baseline cerebral blood flow in humans do not influence regional cerebral blood flow response to photic stimulation.* J Magn Reson Imaging, 2000. 12(5): p. 757-62.**
161. **Barch, D.M., et al., *Anterior cingulate cortex and response conflict: effects of response modality and processing domain.* Cereb Cortex, 2001. 11(9): p. 837-48.**

162. **Barch, D.M., et al., *Anterior cingulate and the monitoriing of response conflict: evidence from an fMRI study of overt verb generation.* J Cogn Neurosci, 2000. 12(2): p. 298-309.**

163. **Braver, T.S., et al., *Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors.* Cereb Cortex, 2001. 11(9): p. 825-36.**

164. **Braver, T.S. and S.R. Bongiolatti, *The role of frontopolar cortex in subgoal processing during working memory.* Neuroimage, 2002. 15(3): p. 523-36.**

165. **Braver, T.S., et al., *A parametric study of prefrontal cortex involvement in human working memory.* Neuroimage, 1997. 5(1): p. 49-62.**

166. **Carter, C.S., et al., *Anterior cingulate cortex, error detection, and the online monitoring of performance.* Science, 1998. 280(5364): p. 747-9.**

167. **Cohen, J.D., et al., *Temporal dynamics of brain activation during a working memory task.* Nature, 1997. 386(6625): p. 604-8.**

168. **Zacks, J.M., et al., *Human brain activity time-locked to perceptual event boundaries.* Nat Neurosci, 2001. 4(6): p. 651-5.**

169. **Cox, R.W., *AFNI:Software for analysis and visualization of functional magnetic resonance neuroimages.* Computers and Biomedical Research, 1996. 29: p. 162-173.**

170. **Cohen, M.S., *Parametric analysis of fMRI data using linear systems methods.* Neuroimage, 1997. 6(2): p. 93-103.**

171. **Buckner, R.L., *Event-related fMRI and the hemodynamic response.* Hum Brain Mapp, 1998. 6(5-6): p. 373-7.**

172. **Buckner, R.L., et al., *Functional-anatomic study of episodic retrieval. II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis.* Neuroimage, 1998. 7(3): p. 163-75.**

173. **Buckner, R.L., et al., *Functional-anatomic correlates of object priming in humans revealed by rapid presentation event-related fMRI.* Neuron, 1998. 20(2): p. 285-96.**

174. **Clare, S., et al., *Detecting activations in event-related fMRI using analysis of variance.* Magn Reson Med, 1999. 42(6): p. 1117-22.**

175. **McCarthy, G., *Event-related potentials and functional MRI: a comparison of localization in sensory, perceptual and cognitive tasks.* Electroencephalogr Clin Neurophysiol Suppl, 1999. 49: p. 3-12.**

176. **Ni, W., et al., *An event-related neuroimaging study distinguishing form and content in sentence processing.* J Cogn Neurosci, 2000. 12(1): p. 120-33.**

177. **Pollmann, S., et al., *Event-related fMRI: comparison of conditions with varying BOLD overlap.* Hum Brain Mapp, 2000. 9(1): p. 26-37.**

178. **Rosen, B.R., R.L. Buckner, and A.M. Dale, *Event-related functional MRI: past, present, and future.* Proc Natl Acad Sci U S A, 1998. 95(3): p. 773-80.**

179. **Kesterson, J. and N. Clinch, *Metabolic rate, respiratory exchange ratio and apneas during meditation.* American Physiological Society, 1989. 89: p. R632-R638.**

180. **Kruger, G., et al., *Simultaneous monitoring of dynamic changes in cerebral blood flow and oxygenation during sustained activation of the human visual cortex.* Neuroreport, 1999. 10(14): p. 2939-43.**

181. **Cao, Y., et al., *Cortical language activation in stroke patients recovering from aphasia with functional MRI.* Stroke, 1999. 30(11): p. 2331-40.**

182. **Cao, Y., et al., *Functional MRI-BOLD of brainstem structures during visually triggered migraine.* Neurology, 2002. 59(1): p. 72-8.**

183. **Huang, J., T.H. Carr, and Y. Cao, *Comparing cortical activations for silent and overt speech using event-related fMRI.* Hum Brain Mapp, 2002. 15(1): p. 39-53.**

184. **Friston, K., *Statistical Parametric Mapping and Other Analyses of Functional Imaging Data*, in *Brain Mapping, The Methods*, A.W. Toga and J.C. Mazziotta, Editors. 1996, Academic Press: New York.**

185. **Cohen, M.S. and R.M. DuBois, *Stability, repeatability, and the expression of signal magnitude in functional magnetic resonance imaging.* J Magn Reson Imaging, 1999. 10(1): p. 33-40.**

186. **Friston, K.J., A.P. Holmes, and K.J. Worsley, *How many subjects constitute a study?* Neuroimage, 1999. 10(1): p. 1-5.**

187. **Litscher, G., et al., *Effects of QiGong on brain function.* Neurol Res, 2001. 23(5): p. 501-5.**

188. **Mann, J.J., et al., *Positron emission tomographic imaging of serotonin activation effects on prefrontal cortex in healthy volunteers.* J Cereb Blood Flow Metab, 1996. 16(3): p. 418-26.**

189. **Peyron, R., B. Laurent, and L. Garcia-Larrea, *Functional imaging of brain responses to pain. A review and meta- analysis (2000).[In Process Citation].* Neurophysiol Clin, 2000. 30(5): p. 263-88.**

190. **Banich, M.T., et al., *Prefrontal regions play a predominant role in imposing an attentional 'set': evidence from fMRI [In Process Citation].* Brain Res Cogn Brain Res, 2000. 10(1-2): p. 1-9.**

191. **Brown, G.G., et al.,** ***Brain activation and pupil response during covert performance of the Stroop Color Word task.*** **J Int Neuropsychol Soc, 1999. 5(4): p. 308-19.**
192. **Ahlfors, S.P., et al.,** ***Spatiotemporal activity of a cortical network for processing visual motion revealed by MEG and fMRI.*** **J Neurophysiol, 1999. 82(5): p. 2545-55.**
193. **Allison, J.D., et al.,** ***Functional MRI cerebral activation and deactivation during finger movement.*** **Neurology, 2000. 54(1): p. 135-42.**
194. **Ardekani, B.A. and I. Kanno,** ***Statistical methods for detecting activated regions in functional MRI of the brain.*** **Magn Reson Imaging, 1998. 16(10): p. 1217-25.**
195. **Ball, T., et al.,** ***The role of higher-order motor areas in voluntary movement as revealed by high-resolution EEG and fMRI.*** **Neuroimage, 1999. 10(6): p. 682-94.**
196. **Beauregard, M., et al.,** ***The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm.*** **Neuroreport, 1998. 9(14): p. 3253-8.**
197. **Booth, J.R., et al.,** ***Functional organization of activation patterns in children: whole brain fMRI imaging during three different cognitive tasks.*** **Prog Neuropsychopharmacol Biol Psychiatry, 1999. 23(4): p. 669-82.**
198. **Bosch, V.,** ***Statistical analysis of multi-subject fMRI data: assessment of focal activations.*** **J Magn Reson Imaging, 2000. 11(1): p. 61-4.**
199. **Buchel, C., et al.,** ***Brain systems mediating aversive conditioning: an event-related fMRI study.*** **Neuron, 1998. 20(5): p. 947-57.**
200. **Kazui, H., H. Kitagaki, and E. Mori,** ***Cortical activation during retrieval of arithmetical facts and actual calculation: a functional magnetic resonance imaging study [In Process Citation].*** **Psychiatry Clin Neurosci, 2000. 54(4): p. 479-85.**
201. **Ramsay, S.C., et al.,** ***Changes in global cerebral blood flow in humans: effect on regional cerebral blood flow during a neural activation task.*** **J Physiol (Lond), 1993. 471: p. 521-34.**
202. **Schwarzbauer, C. and W. Heinke,** ***Investigating the dependence of BOLD contrast on oxidative metabolism.*** **Magn Reson Med, 1999. 41(3): p. 537-43.**
203. **Kastrup, A., et al.,** ***Assessment of cerebral oxidative metabolism with Breath-Holding and fMRI.*** **Magn Reson Med, 1999. 42(3): p. 608-11.**
204. **Kastrup, A., et al.,** ***Functional magnetic resonance imaging of regional cerebral blood oxygenation changes during Breath-Holding.*** **Stroke, 1998. 29(12): p. 2641-5.**
205. **Kastrup, A., et al.,** ***Cerebral blood flow-related signal changes during breath-holding.*** **AJNR Am J Neuroradiol, 1999. 20(7): p. 1233-8.**
206. **Kastrup, A., et al.,** ***Regional variability of cerebral blood oxygenation response to hypercapnia.*** **Neuroimage, 1999. 10(6): p. 675-81.**
207. **Smejkal, V., R. Druga, and J. Tintera,** ***Control of breathing and brain activation in human subjects seen by functional magnetic resonance imaging.*** **Physiol Res, 1999. 48(1): p. 21-5.**
208. **Talairach, J. and P. Tournoux,** ***Co-planar Stereotaxic Atlas of the Human Brain. A 3-D Proportional System: An Approach to Cerebral Imaging*****. 1988, New York: Thieme Publishers.**
209. **Kwong, K.K., et al.,** ***EPI imaging of global increase of brain MR signal with breath-hold preceded by breathing O2.*** **Magn Reson Med, 1995. 33(3): p. 448-52.**
210. **Manning, H.L., et al.,** ***Reduced tidal volume increases 'air hunger' at fixed PCO2 in ventilated quadriplegics.*** **Respir Physiol, 1992. 90(1): p. 19-30.**
211. **Davis, C.P., et al.,** ***Ultra-high-speed MR imaging.*** **Eur Radiol, 1996. 6(3): p. 297-311.**