Study Title: Managing Pain and Cognitions in Older Adults With Mild Cognitive Impairment or Memory Related Problems and Chronic Pain

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I. BACKGROUND AND SIGNIFICANCE

1.1 Chronic pain and Mild Cognitive Impairment (MCI) are highly prevalent among older adults and independently associated with decreased emotional and physical function. Approximately one third of older adults experience pain daily[5]. In older adults, chronic pain is associated with substantial disability from reduced mobility, avoidance of activity, falls, depression and anxiety, sleep impairment, and isolation[7–10]. Its negative effects extend beyond the patient, to disrupt both family and social relationships. Patients with chronic pain also report non-adaptive coping strategies with pain catastrophizing and fear of pain being the most salient, and both associated with decreases in physical and emotional function[25–28]. Prevalence rates for pain are expected to increase as populations continue to age—by 2035 an estimated one quarter of the population in the European Union will be 65 or older—thereby increasing the public health impact of pain[29]. As a consequence, NCCIH has designated chronic pain as a national priority area[4]. Mild cognitive impairment (MCI) – a decline in cognitions, including memory, communication, concentration and orientation over what is considered normal aging, is also prevalent, with 1 in 5 older adults reporting symptoms of MCI[6]. MCI is the intermediate stage between the cognitive changes of normal aging and dementia. Individuals diagnosed with MCI show cognitive impairment greater than expected for their age, but otherwise are functioning independently and do not yet meet the criteria for dementia[30]. MCI is associated with decreased mobility, and physical function[31], and high distress[32.]

1.2. There are no evidence based nonpharmacological treatments to address chronic pain in older adults with MCI. MCI and chronic pain are highly comorbid, with rates up to 45% in primary care clinics[33]. At the Massachusetts General Hospital Memory Disorders Unit (aka Memory Clinic), over 50% of patients with MCI also have chronic pain. Presence of both MCI and chronic pain has an even greater impact on physical and emotional functioning than either of these conditions separately[34]. In addition, pain has independent, negative effects on cognitive functioning[11]. Despite this evidence, no nonpharmacological treatments exist to directly target physical and emotional functioning in patients with MCI who also have chronic pain. As such, we need to develop novel nonpharmacological pain management strategies that are less reliant on cognitive skills, are developed with input from MCI older adults, and are specifically tailored for the needs of patients with chronic pain and MCI.

1.3. Mind body programs show promise with chronic pain and with MCI, but fail to improve physical function. Over the last decade, psychosocial treatments have evolved toward acceptance of pain and increased function regardless of pain sensations[35–37]. Mind body programs such as Acceptance and Commitment Therapy (ACT) and Mindfulness Skills Training (MST) programs focus on engaging in value driven behaviors, even if those are painful[37–40]. With less emphasis on cognitive skills, MST have also been shown to be feasible and highly beneficial in older adults with MCI[41]. However, these interventions produce only small to moderate effect sizes for psychosocial outcomes like depression, anxiety, stress, and overall quality of life and effects diminish over time[42]. Further, although IMMPACT[12,43] recommendations clearly specify that physical function should be a required outcome in pain and MCI clinical trials, few studies include it ; when physical function is included as an outcome, effect sizes are small and fade over time[37,44].. Thus, there is a need for novel interventions to directly target improvement in physical functioning in patients with chronic pain and MCI.
Physical function, defined following the ICF[13], implies "a person's capacity in a set of situations and includes engagement in meaningful aspects of one's life including performing activities of daily living such as household chores, walking, work and self care" and is consistently associated with mental and physical health benefits[45]. New recommendations from IMMPACT released during the summer of 2016[12] focus primarily on physical function, and urge researchers to directly target it during pain clinical trials as well as to conceptualize it comprehensively through self report measures of activity of daily living and physical activity (biased due to perceptions but important to patients), performance based measures (e.g., walk test; still subject to bias due to motivation and perceptions), and more objective measures of physical activity such as accelerometers or other digital monitoring devices like the Fitbit (which are valid and comparable to live observations of activity). **No mind body studies in chronic pain or MCI to date have comprehensively addressed and assessed physical function/activity consistent with ICF[13] and IMMPACT[12] 2016 criteria.** This represents an unexplored opportunity to improve outcomes and sustain improvements in this population.

1.4. Quota based walking is associated with improved outcomes in chronic pain patients and older adults, but is not incorporated within mind body programs. The US Department of Public Health's research has shown a clear

relationship between daily physical activity such as a 30-minute walk and several health related outcomes such as mortality, cardiovascular diseases and cancer[46]. Patients with chronic pain and MCI are sedentary and take significantly fewer steps per day than an average healthy adult[47–50]. Although exercise is one of the recommended treatments for MCI patients with documented cognitive benefits, few successfully engage in these programs[51]. Deconditioning is common in chronic pain, can be a significant risk factor for *further* pain conditions and disability[50]. Aerobic exercise has been shown to be the mainstay of chronic pain treatments for multiple, heterogeneous pain conditions including low back pain, fibromyalgia, and chronic myofascial conditions, with walking being the most commonly prescribed, but adherence being problematic[49,50,52]. When walking is quota-based (i.e., not contingent on pain level), results are even more promising[53–55.] Prior research has identified barriers to engaging and adhering to physical exercise in chronic pain, which included decreased mood, pain, coping difficulties (e.g., fear avoidance, catastrophic thinking about pain), programs that were too challenging (e.g., going to the gym), not meaningful, interfering with one's life, or too difficult to implement[56–59]. Focus groups and qualitative interviews with older adults with chronic pain have consistently showed that walking is the preferred method of physical activity in this population[57]. **Despite the aforementioned benefits of physical activity for chronic pain and MCI physical activity including walking are not addressed or assessed in mind body programs**.

1.5. Digital monitoring devices (DMDs) simultaneously reinforce and assess objective physical function/activity while maintaining motivation and safely increasing physical activity, and are feasible to use with older populations. Digital monitoring devices can make tracking activity in healthcare more convenient, accurate and cost effective for patients. Pedometers are associated with a significant increase in physical activity and decrease in body mass and blood pressure[58,60]. Piezoelectric accelerometers measure proper acceleration ("g-force") and already have several clinical applications including validating self-report measures, assessing physical function via expended energy (EE) in different populations, as a novel way for clinicians to track physical activity and as a potential motivator for behavior, treatment alliance and adherence[21,22,61]. Although pedometers and accelerometers have been around for a long time[60,62], long term adherence to their use has been problematic, and the lack of real time feedback has limited their ability to act as an intervention[63,64]. With the miniaturization of these devices and the advent of low energy Bluetooth 4.0 peripheral devices such as FitBit DMD, patients can now track their activity and receive real time feedback to increase motivation and reinforce activity. Fitbit DMDs represent an opportunity to directly measure objective physical functioning/activity, while actively reinforcing the patient in incremental, quota-based gains in activity that are individualized to each patient's ability and gradually increased[24]. They have been successfully used with older adults[22,65,66,] while documentation of their adoption to chronic pain or MCI adults has been through only anecdotal case reports. **DMDs represent an unexplored opportunity to objectively measure, target and reinforce improvements in physical activity/function in adults with chronic pain and MCI.**

1.6. Combining mind body programs with the Fitbit DMD represents an opportunity to directly target increased physical activity and improve physical and emotional outcomes in older adults with MCI and chronic pain. Mind body programs teach patients skills that can address some of the barriers to engaging and adhering to activity delineated above such as low mood, over focus on control of pain rather than acceptance, fear avoidance and non-adaptive thoughts about pain. Fitbit DMDs can provide real time reinforcements that can increase motivation and enhance adherence. Further, physical activity can be individualized based on patient's interest and paired with activities of daily living that are meaningful to participants and fit individual schedules, further decreasing barriers to engagement in exercise programs identified in prior research[56,57,59.]

1.6. The Relaxation Response Resiliency Program (3RP[14]) is a comprehensive, multimodal mind body group based program that lends itself to the incorporation of the DMD. The 3RP is a novel multimodal mind body intervention that combines relaxation response (RR) elicitation strategies (e.g. mindfulness, meditation) with increased awareness of emotional, cognitive, physical, behavioral and relational correlates of stress and symptoms and adaptive strategies such as positive perspectives, reappraisals and coping, social support and healthy lifestyle behaviors. All components of the 3RP have been individually found efficacious in improving outcomes in prior research[40,42,67,68.] Multimodal programs that incorporate a variety of skills (as the 3RP does) are more efficacious than unimodal programs[69]. The 3RP, a skills based multimodal treatment program, is a perfect fit for adaptation for chronic pain management including addressing increased activity aided by the DMD to address comprehensively physical function, consistent with IMMPACT recommendations. Justification for using the 3RP: 1) it is a multimodal program consistent with recommendations for research in chronic pain[69]; 2) has built in SMART (Specific, Measurable, Attainable, Realistic and Time based) goal setting in each session thus providing a built in framework for setting goals for increased activity paired with activities of daily living that are meaningful to patients and monitoring through DMDs. 3) teaches evidenced based skills that were previously found

promising in medical populations including chronic pain[40,42,67,68] when tested individually; 4) it has embedded educational information on the positive role of physical activity for healthy lifestyle; 5) it is designed to help patients adjust to chronic symptoms, rather than eliminate them, which is consistent with IMMPACT[12]; 6) the program accommodates a 6th grade reading level allowing for patients with low health literacy or learning disabilities; 7) it has evidence of high feasibility and acceptability in effectiveness studies[15–18,20] and a recent preliminary RCT[20].; 9) has been successfully used with older populations[70,71]; 8) it has an already developed time and dose matched attention placebo educational control, The Health Enhancement Program (HEP)[72], that has already been adapted for pain and is currently used with 80% feasibility in the Pain Clinic at MGH.

1.7. Preliminary research with the 3RP is encouraging. The 3RP has evolved over the years from its inception as Medical Symptom Reduction Program to its current standardized form. Effectiveness and pilot studies have found that including older adults[71]. The 3RP was also found to have high adherence and improve pain intensity, frequency, tolerability and objective functioning in an open pilot with patients with refractory chronic mandibular join disorder[18], and improve psychoemotional variables and pain catastrophizing in patients with neurofibromatosis[19,20]. In a RCT of the 3RP versus an attention placebo control HEP, Vranceanu et al.[20] found 100% adherence in both groups and significant improvement in both physical health and psychological quality of life in the 3RP group, which was over the minimal clinically important difference (MCID). Further, in patients with moderate and severe pain there was a decrease in both pain intensity and pain interference in the 3RP group, which were over the MCID. The 3RP is currently being tested in large RCT in medical populations such as multiple myeloma (PI: Denninger) and patients with comorbid PTSD and respiratory problems (PI: Gonzalez). Further, large RCTs of the 3RP are currently under review with NIH (e.g., U01NS102183 NINDS, Vranceanu PI; NINR Donelly PI) and DOD (PI: Vranceanu).

1.8. Using the NCCIH R34 we have already adapted the 3RP for the needs of patients with chronic pain. In year 1 of our current R34 we have conducted focus groups with adults with chronic pain (N=24) , and, using this information and our multidisciplinary team, we have developed the GetActive (3RP that addresses the needs of patients with chronic pain and increased physical activity) and GetActive with Fitbit (3RP that addresses the needs of patients with chronic pain and increased physical activity using the Fitbit), and conducted an open pilot of each of the 2 programs in adults with chronic pain. So far, feasibility, acceptability and adherence have been excellent. Patients in the GetActive with Fitbit have all been able to gradually increase their number of steps for the first 5 weeks of the program. However, additional adaptations are required in order for these programs to directly address the needs of older adults with MCI or MRP. We plan to use this successful methodology to conduct adaptations of the GetActive and Get Active with Fitbit for the specific needs of older adults who have chronic pain and MCI or MRP.

1.19. Summary and scientific promise: This supplement addresses an important research gap – the need to develop nonpharmacological interventions targeting chronic pain in older individuals with MCI or MRP. Currently, there are no treatments available for this population. Using the NCCIH R34 mechanism and following recommendations from IMMPACT[12], ICH[13] and prior systematic reviews in chronic pain trials[43,73], our multidisciplinary team proposes to further develop, adapt and refine the GetActive and GetActive with Fitbit (including the existent manuals that we developed in year 1 of our R34) for the specific needs of patients with MCI or MRP who also have chronic pain (*Active Brains and* ***Active Brains-Fitbit.*** **The goal is to maximize the feasibility, acceptability, credibility and adherence of the both programs tailored for the needs of older adults with chronic pain and MCI or MRP, of a fully powered RCT of the *Active Brains* versus *Active Brains-Fitbit* versus a** Health Enhancement Program (HEP) educational control already adapted for pain and integrated in the Pain Clinic at MGH, developed by our team[72].

3.1 Procedures Overview

The present proposal **aimed** to adapt, pilot and examine the credibility, acceptability, adherence and feasibility of the GetActive and GetActive with Fitbit adapted for older adults with MCI or memory-related problems (MRP) (*Active Brains and Active Brains with Fitbit).* We have already developed the GetActive and GetActive-Fitbit which are adapted for the specific needs of patients with chronic pain, but not for older adults with MCI or MRP, who are currently excluded from the R34 study. We now aim to compare *Active Brains–Fitbit* vs an attention placebo control (HEP) in a pilot randomized control trial. Our goal is to compare the credibility, feasibility, usability and adherence between the two programs, *Active Brains-Fitbit* and the HEP, as well as all study procedures in preparation for an efficacy trial. The proposed R34 supplement feasibility project will lay the groundwork for a large RCT of the *Active Brains vs. Active Brains-Fitbit* vs attention placebo control HEP, and will help us understand whether the Fitbit is feasible and necessary to comprehensively improve function. Consistent with prior theory within a subsequent efficacy trial we will test the hypothesis that the *Active Brains-Fitbit* will be superior to the *Active Brains* and *HEP* in improving and sustaining improvements in objective, performance based and self-

reported physical and emotional function in older adults with heterogeneous chronic pain comorbid with MCI or MRP. Using the supplement to the NCCIH R34 mechanism we will follow an iterative design[81,82] to adapt and refine both the (GetActive and GetActive with Fitbit) interventions to maximize feasibility, acceptability, credibility, recruitment protocol, adherence and measurements for patients with heterogeneous chronic pain. To allow objective measurement of activity in both *Active Brains* and *Active Brains-Fitbit* groups, we will use Accelerometer DMDs for 1 week at baseline and post-test. The Fitbit will be used to address/reinforce activity consistent with an individualized pacing plan, and to assess daily activity during the program only for those in the *Active Brains-Fitbit.* All procedures have already been piloted within our NCCIH R34 and will easily be adapted for the supplement.

3.2. Active Brains and Active Brains with Fitbit

In year 1 of the NCCIH R34, Dr. Vranceanu adapted the general GetActive [14] for patients with heterogeneous chronic pain without MCI, including for increased physical activity with or without Fitbit. We will further adapt these programs for the specific needs of older adults with MCI or MRP A description of each of the 8 proposed *Active Brains withFitbit* sessions in comparison with the GetActive-Fitbit are depicted in Table 1. Adaptations for the *Active Brains* will be identical but will not include Fitbit integration adaptations. The GetActive introduces and reinforces new skills through didactics, in-session activities, discussions, and daily home practice assignments. Homework involved setting SMART goals, recording type and amount of daily RR practice, and recording daily 1-3 appreciations. Each session begins with the practice of a new exercise to elicit the RR. The relaxation method is then coordinated with the remaining session content. The main proposed adaptations for older adults with MCI or MRP are: 1) simplification of skills; 2) ensuring that participants write down main points of discussion; 3) focusing on making changes to the environment to make it easy to keep up habits and hard to not keep up habits; 4) involving the caregiver; 5) eliminating skills that focus on cognitive function (e.g., adaptive thinking); 6) elimination of the more complex RR exercises like contemplation and idealized self and replacing those with RR exercises on empathy and acceptance.

Table 1. Session by session adaptations of the general GetActive for chronic pain, increased activity AND Fitbit use.

Nr.	**GetActive** sessions	Proposed ***Active Brains-Fitbit*** (additional skills/discussions, or tailored skills)
1	1. SMART goals 2. Description of Stress Response (SR) vs Relaxation Response (RR) 3. Resiliency 4. Program description 5. In session RR exercises 6. Description of homework: appreciations, SMART goals, RR practice **(repeats every session)**	1. Function specific SMART goal (number of steps tied in with specific value driven activities of daily living such as going to the store, etc). Quota based pacing for effective increase in activity regardless of pain sensations. 2. Example of SR for pain episodes. SR as pain alarm/fear avoidance. 3. Resiliency as pertaining to chronic pain 4. Program description specifically for pain 5. Pain specific RR exercises 6. Identification of meaningful activities to pair with increased number of steps. 7.. Instruction to DMD; prescription to wear and download; Benefits of consistently using the Fitbit DMD 8.. Homework: appreciations, SMART goals, RR practice, how to achieve step goal.
2	1. Review homework/skills 2. Overview of methods to elicit RR 3. Tips for developing a consistent practice 4. Sleep concerns/tips 5. RR elicitation: body scan/breath focus, MINIs 6. Emotions and physical sensations 7. Homework	1. Review homework /skills including activity/DMD adherence 2. Overview of pain specific methods to elicit RR and how to use them to increase activity. 3. Tips for developing a consistent practice and adherence to DMD 4. Barriers to increased activity/exercise. 5. Benefits of physical activity: mental and physical. 6. Sleep concerns/tips/hygiene; pain related barriers to sleep 7. RR elicitation: body scan/breath focus, MINIs 8. Relationship between pain, activity and emotions. 9. Using DMD efficiently to increase activity. 10. Homework; new block for those with 5 days (1 block) adherence and step goal met.
3	1. Review homework/skills 2. RR elicitation: Mindful awareness 3. Components of SR: physical, cognitive, emotional, behavioral, relational 4. Social support	1. Review homework/skills including activity/DMD adherence 2. RR elicitation: Mindful awareness about pain. Using mindfulness to aid with increased numbers of steps. 3. Components of SR for pain episodes/pain alarm: physical, cognitive, emotional, behavioral, relational 4. Awareness of Pain cycle: pain sensations, negative pain thoughts, negative emotions, avoidance of activity, isolation, hypervigilence to pain, amplification of pain sensations, deconditioning, decreased physical function, depression, anxiety, increased pain.

	5. Homework	5. Social support pain specific; friends and partners as solicitous, negative, or supportive without reinforcing pain.
		6. Homework: new block for those with 5 days (1 block) adherence and step goal met.
4	1. Review homework/skills 2. Awareness of movement in daily living 3. Awareness of thoughts 4. Emotions and beliefs 5. Yoga and walking meditation 6. Homework	1. Review homework/skills including activity/ DMD adherence 2. Awareness of movement in daily living; awareness of pain with movement. Walking and pain. 3. Awareness of thoughts; pain related thoughts 4. Emotions and beliefs: pain and activity related emotions and beliefs. 5. Yoga and walking meditation; pain specific alterations and applications. 6. Homework: newblock (step goal) for those with 5 days (1 block) adherence and step goal met.
5	1. Review of homework/skills 2. Guided imagery 3. Creating an adaptive perspective 4. RR; Joyful place; MINIs: Stop, Breath, Reflect, Choose. 6. Homework	1. Review of homework/skills including activity/DMD adherence. 2. Guided imagery; pain specific; coping with pain flare-ups 3. Creating an adaptive perspective; pain specific, interpreting pain sensations as noncancerous, continuing activity (e.g., walking) consistent with step goal in spite of pain sensations, sitting with negative emotions and watching them dissipate, decreased hypervigilence to pain, habituation to pain sensations, increase comfort with pain sensations, increased muscle tone and physiological adaptations, increase in activities of daily living, increase physical function, decreased depression and anxiety. 4. RR; Joyful place; 5. MINIs: Stop, Breath, Reflect, Choose; adaptations for communication, medical care, relationship, work, and pain. 6. Homework: new block for those with 5 days (1 block) adherence and step goal met.
6	1. Review of homework/skills 2. Loving kindness meditation 3. Cultivating optimism 4. RR signals 5. Homework	1. Review of homework/skills including DMD adherence. 2. Loving kindness meditation 3. Cultivating optimism during pain flare-ups or decreased activity. 4. How to get back on track after a lapse in activity. 4. RR signals and pain and activity. 5. Homework: new block (step goal) for those with 5 days (1 block) adherence and step goal met.
7	1. Review of homework/skills 2. Acceptance and problem solving 3. Empathy 4. Contemplation 5. Homework	1. Review of homework/skills including DMD adherence. 2. Acceptance of emotions and physical sensations including pain at rest or withactivity. Acceptance of pain as a chronic condition. 3. Empathy: self and others 4. Contemplation of the chronic pain experience and instilling posttraumatic growth (.e.g., lessons in empathy, resilience, self awareness, mastering skills). 5. Homework: new block for those with 5 days (1 block) adherence and step goal met.
8	1. Review of homework/ and all skills 2. Humor and coping 3. Tips for staying resilient 4. Idealized self	1. Review of homework/skills including activity/DMD adherence 2. Humor and coping for pain 3. Tips for staying resilient during pain flares, episodes, hard time. 4. Idealized self – visualizing using coping skills for life. 5. Review of all skills/plan for continuing to use the DMD and pain coping skills.

Adaptations for the *Active Brains* will follow the same framework without any of the Fitbit specific adaptations. All adaptations will occur after input from patients through the focus groups.

II. SPECIFIC AIMS

Specific aims for phase I are:

The aim of this project is to develop and pilot test the first mind body program targeting chronic pain in older adults with mild cognitive impairment (MCI) or memory-related problems (MRP). In phase I we will propose adaptations to an evidence based mind body program that targets chronic pain and increased physical activity without (GetActive) or with (GetActive-Fitbit) a commercially available digital monitoring device Fitbit, for the unique needs of older adults diagnosed with mild cognitive impairment (MCI) or memory-related problems (MRP). We will conduct 2-3 focus groups with patients, 2-3 with caregivers, for a total of 4-6 focus groups (N = 30 patients/30 caregivers). There will be 60 participants total.

Aim 1, Step 1: In the first step our multidisciplinary team will propose modifications to the Active Brains and *Active Brains-**Fitbit*** to address the needs of older adults with chronic pain and MCI reported in the literature. Based on this information, we will develop a semi-structured qualitative interview script.

Hypotheses: NA

Aim 2, Step 2: In the second step, we will use the semi-structured qualitative interview to guide 2-3 focus groups (N = 30) with patients to gather feedback on the intervention components, gauge treatment needs and expectations, as well as barriers and ways to facilitate participation in the intervention and adherence to the use of Fitbit and mind body specific practice, among older adults with chronic pain and MCI or MRP. In addition, we will develop a semi-structured interview qualitative script for caregivers of patients with chronic pain and MCI or MRP and will conduct 2-3 focus groups (N = 30) with caregivers. The feedback from caregivers will help to better serve patients with chronic pain and mild cognitive impairment. Patients will also complete a demographic and self-report questionnaire and will be administered a test of cognitive functioning (MOCA). Caregivers will also complete a brief demographic and self-report questionnaire after the focus group. All participants will also be able to complete an additional, optional battery of questionnaires assessing pain, function, cognitions and emotions, either in person or over the phone, the same day or at a time that is convenient for them.

Hypotheses: NA

Specific aims for phase II are:

Aim 2: We will conduct 2 nonrandomized open pilots (30 patients total, 15/arm) of the refined *Active Brains-Fitbit* versus the refined Active Brain for patients with chronic pain and MCI or MRP. We will collect quantitative survey and exit interview data about feasibility, acceptability, and credibility. We will also compare the credibility, feasibility, usability and adherence between the 2 treatments as well as all study procedures in preparation for an efficacy trial.

Specific aims for phase III are:

Aim 3: We will conduct a virtual randomized controlled trial of the Active Brains-Fitbit program versus an education control (Health Enhancement Program) in chronic pain patients with MCI or MRP (N = 40 total; 5-8/group). We will collect quantitative survey and exit interview data about feasibility, acceptability, and credibility. We will use data to further refine the programs. We will compare the credibility, feasibility, usability and adherence between the two programs, *Active Brains-Fitbit* and the HEP, as well as all study procedures in preparation for an efficacy trial.

III. SUBJECT SELECTION

Participants will be recruited among patients with MCI or MRP and chronic pain who present to the Memory Clinic or the Pain **Clinic** at the Massachusetts General Hospital or PAC and meet study criteria. We have support from the Memory Clinic and the Pain Clinic with recruitment, and have budgeted research assistant time to facilitate enrollment on site. Physicians will first inform the eligible patients (with MCI or MRP and chronic pain) about the study and give them study flyers. Participants will be new patients presenting to Partners-affiliated medical practices for memory or pain, or patients presenting to Boston area pain and memory centers and medical practices that treat chronic pain patients and meet study criteria. Participants may hear about the study from Rally or recruitment flyers with tear-off research coordinator contact information that will be posted in the hospital and at referral sites. Our IRB approved flyers will also be posted to memory related groups (e.g. open forums for MCI, Facebook groups for individuals with memory problems and their loved ones) online. We will post to publicly accessible groups, as well as moderated groups. We will review and comply with group guidelines prior to posting our study advertisement. A research assistant will reach out to the participant by phone or by email. A research assistant will provide study details to interested participants and screen for eligibility; those who wish to participate will complete the informed consent process. Participants will be asked to self-report if they have any memory problems, such as problems forgetting names, events, getting lost, or having to re-read information over and over. If necessary, we will also ask if others have noted that the participant has had these challenges. (Phase I only): We will first recruit patients and then ask if they have a caregiver that may be willing to participate. If the patient is referred in-clinic, we will only contact the caregiver if the patient gives permission. Patients without a caregiver are still eligible to attend the focus groups. Caregivers have the opportunity to contact the study staff through our Rally advertisement. Caregivers without a patient (e.g. patient screens out) are still eligible to attend the focus groups. These procedures will be done in a private setting, and will not impact in any way the delivery of care within the practice. This strategy has been used successfully in prior studies conducted by the PI. Subjects will be older adult

(age 60 or older) patients with a MCI or MRP, who also have chronic pain (pain present for 3 months or longer). Caregivers will only be recruited during Phase I.

Recruitment will also occur through the Research Patient Database Registry (RPDR). The RPDR is a centralized clinical data registry that gathers data from various hospital legacy systems and stores it in one place. Researchers access the data using the RPDR online Query Tool. They may query the RPDR data for aggregate totals, and with proper IRB approval, obtain medical record data. The RPDR ensures the security of patient information by controlling and auditing the distribution of patient data within the guidelines of the IRB and with the use of several built-in, automated security measures. To identify potentially eligible patients:

1) A RPDR query will be performed to identify those patients with chronic pain diagnoses. Study staff will review the medical record to confirm potential participant eligibility and to identify their linkage to an MGH primary care physician. Access to patients' medical records will be restricted to this pre-enrollment recruitment phase.
2) Study staff then will obtain permission for initial contact from each potentially eligible patient's PCP by having providers review letters and discard ones that they do not approve.
3) For physician-approved patients, study staff will send a study introduction letter from the patient's physician (with the clinician's name at the bottom) and a study opt-out letter signed by Ana-Maria Vranceanu (PI). The letter from the PCP informs the patient that he or she is allowing the study to contact patients with chronic pain in case they are interested in learning about the study. Dr. Vranceanu's letter is an opt-out letter describing the study, the procedure to opt out of further contact, and whom to call for further information.
4) Should study staff receive no reply within 10 days, staff members will call the patient on the phone to assess interest in the study and to describe the study over the phone. If the patient remains interested, staff will confirm eligibility and assess for inclusion and exclusion criteria.
5) For potentially eligible patients who are enrolled in the MGH Research Options Direct to You (RODY) Program, we will send them an opt-out letter and call 10 days later to inform them about the study. RODY identifies patients who are willing to be contacted directly about research studies. Patients who have agreed to be contacted directly are identifiable through the RPDR search; each patient's RODY status is available in the demographics table included in the RPDR output.

A research assistant will provide study details to interested participants and screen for eligibility; those who wish to participate will complete the informed consent process. These procedures will be done in a private setting over the phone, and will not impact in any way the delivery of care within the practice. This strategy has been used successfully in prior studies conducted by the PI. Data will be collected in MGH Integrated Brain Health Clinical and Research Program and will be managed and analyzed collaboratively by investigators at MGH.

4. Feasibility The Memory Clinic at MGH is a busy clinical and research practice. The Center has approximately 498 patients with MCI who are seen yearly for care. Of these, approximately 50% are chronic pain patients. As such, we can be confident that we will be able to identify and recruit the necessary number of participants. However, if any recruitment difficulties occur, we will be able to recruit participants from Brigham and Women's Hospital's Memory Clinic.

IV. SUBJECT ENROLLMENT

Interested participants who meet study criteria will be consented and then scheduled to participate in one of the focus groups (in Phase I) or intervention groups (in Phase II). See Table 1.

Table 1	
Patient Inclusion Criteria	**Rationale**
Male and female outpatients, age 60 years or older	Population under study
Have nonmalignant chronic pain for more than 3 months	International Association for Study of Pain (IASP)[1] criteria

Has MCI or memory-related problems (MRP) (forgetting names, getting lost, forgetting obligations)	Population of study
Able to perform a 6-minute walk test at an accelerated pace	Program will involve increase number of steps/outcome measure
Free of concurrent psychotropic or pain medication for at least 2 weeks prior to initiation of treatment, OR stable on current psychotropic or pain medication for a minimum of 6 weeks and willing to maintain a stable dose	Treatment confound
Cleared by a medical doctor for study participation	Human subject concern, risk
Owns a smartphone with Bluetooth 4.0	Necessary for pairing with DMD and storing/downloading data.
Caregiver Inclusion Criteria (Phase I only)	**Rationale**
Caring for someone with mild cognitive impairment and chronic pain	Population of study
Currently living with someone with mild cognitive impairment and chronic pain	Population of study
Patient Exclusion Criteria	**Rationale**
Diagnosed with a medical illness expected to worsen in the next 6 months (e.g., malignancy)	Treatment confound
Serious mental illness or instability for which hospitalization may be likely in the next 6 months	Feasibility, participant safety
Current suicidal ideation reported on self-report	Subject safety
Lifetime history of schizophrenia, bipolar disorder, or other psychotic disorder	Treatment confound
Current substance abuse or dependence and current substance use disorder, within the past 6 months	Treatment confound
Practice of yoga/meditation, or other mind body techniques that elicit the RR, once per week for 45min or more within the last 3 months or less	Treatment confound
Regular use of Fitbit in the last 3 months.	Treatment confound
Engage in regular intensive physical exercise for more than 30 minutes a day	Treatment confound
Unable to walk without use of assistance (e.g. walker, cane, wheelchair)	Treatment confound

STUDY PROCEDURES

Phase I:

In the first step our multidisciplinary team will propose modifications to the general GetActive and GetActive with Fitbit to address the needs of older adults with chronic pain and MCI reported in the literature, with a focus on adaptation of skills for the challenges faced by MCI or MRP patients, including the use of environmental reinforcers (e.g., caregivers, reminders) to aid with skill acquisition and maintenance. Based on this information, we will adapt the semi-structured qualitative interview script we used in the previously established program (R34) for patients and caregivers of patients. We will introduce and demonstrate the main skills of the mind body program and gather feedback on proposed modification and usability of each skill. In the second step, we will use the semi structured qualitative interview to guide 2-3 focus groups (N = 30 total) with patients to gather feedback on the intervention components, gauge treatment needs and expectations, as well as barriers and

ways to facilitate participation in the intervention and adherence to the use of *Active Brains and* ***Active Brains-Fitbit*** specific practice, among older adults with chronic pain and MCI or MRP. In addition, we will develop a semi-structured interview qualitative script for caregivers of patients with chronic pain and documented MCI or MRP and will conduct 2-3 focus groups (N = 30) with caregivers. The feedback from caregivers will help to better serve patients with chronic pain and mild cognitive impairment. Patients will also complete a brief demographic and self-report questionnaire and will be administered a test of cognitive functioning (MOCA). The MOCA will be administered by a trained research assistant. Caregivers will also complete a demographic and self-report questionnaire after the focus group. They will not be asked to complete the MOCA. All participants will be given the option to complete an additional, longer (30-45 minutes) questionnaire either in person or over the phone at a time that is convenient for each participant. All information shared in the focus groups will be recorded.

Focus group script (will be finalized in aim 1).

Exit interview (will be finalized in aim 2).

End of phase 1 deliverables: 1) develop the Active Brains and Active Brains-Fitbit through adapting GetActive and GetActive with Fitbit interventions/manuals to address the needs of patients with MCI or MRP); 2) identify/problem solve potential barriers to adherence to homework and Fitbit use during the duration of the program, and Accelerometer use for baseline and posttest assessments, including acceptability, credibility, feasibility, recruitment and adherence; 3) solidify inclusionary and exclusionary criteria and 4) finalized instruments to use in phase 2. We will use "lessons learned" from the year 1 activities of the R34 (focus groups and open pilot groups) to facilitate activities in phase 1. ***At the end of this phase we will have 2 interventions: Active Brains (GetActive adapted for MCI) and Active Brains-Fitbit (GetActive with Fitbit adapted for MCI).***

Phase II:
After enrollment, participants will be asked to attend one of the two intervention groups, *Active Brains* or ***Active Brains-Fitbit*** (N=30) in an open pilot. Participants will have either a choice of either the *Active Brains* or ***Active Brains-Fitbit*** one group is full; the remaining participants will then be assigned to the available group. The intervention groups will be conducted in person at MGH by trained study therapists over 10 weeks. Participants will complete demographic questions, baseline psychological and behavioral questionnaires, a cognitive assessment administer by a trained study staff, and an exit interview. Interview domains will include: 1) satisfaction with the intervention, 2) areas that were most helpful, 3) areas that were least helpful, 4) ways to improve the intervention and its acceptability (e.g. satisfaction, fit of the intervention within daily life, confidence in treatment and therapist), 5) perceived increase in self-report, objective and performance function.

Participants will also give feedback about the assessments and whether they capture aspects important to them, and we will refine the length, timing, and content of these as needed. We will ask specific questions about any problems with adherence to *Active Brains* and *Active Brains-Fitbit* homework. Questions will also be asked about the therapeutic alliance with the group leader, and the extent to which participants felt connected and understood by the group leader. Finally, we will ask questions about the best approaches for participant recruitment and retention. Dr. Vranceanu has used these types of procedures in other mind-body intervention studies. Information from qualitative interviews will be corroborated with information from the satisfaction and the credibility questionnaires and will serve to refine the intervention for the next phase.

During enrollment, participants have the option to consent to receiving reminders in the form of phone calls, text messages, or email over the course of the intervention, depending on personal preference. Participants will be informed of texting risks and provide consent for text messaging in writing or verbally if preferred. Participants will have the opportunity to ask questions about texting with study staff. Approval of text messaging and/or opting out of text messaging will be recorded in each participants file. Between session contact will be used with the goal of increasing treatment adherence and engagement and session reminders. Text messages will be sent once or twice a week for the duration of the study. Participants may opt-out of the text message contact option at any point.

Participants in the *Active Brains-Fitbit* group will pair their Fitbit DMD to a smartphone with Bluetooth, and the Fitbit will inform an individualized quota-based behavioral plan to improve both adherence and efficacy. All participants will also wear an accelerometer for 7 days at baseline and at the end of the intervention. Participants will be compensated $30 for each assessment completed, and $10 for transportation (for each visit). Participants may earn up to $160.

Phase III:

Prior to enrollment, interested participants will contact study staff for more information about participation. A research assistant will provide study details to participants and screen for eligibility via phone. Participants will be asked to self-report if they have any memory problems, such as problems forgetting names, events, getting lost, or having to re-read information over and over, as well as their future availability to attend the program. Additionally, those who express interest and wish to participate in the study will review the consent form briefly with a member of study staff via phone during the initial screening conversation. The study staff will continue to follow-up with interested participants via phone until a date for the groups have been selected (group times are based off the majority of participants' availability). Once a date and time for the groups has been selected, a member of study staff will email participants the consent form 2-3 weeks prior to the baseline session.

After consenting, participants will set up a time with a member of study staff to download Zoom and to learn how to use the platform, in order to see all participating members of the group. Zoom specifically states that their software is equipped to keep information secure and the software does not have access to identifiable information. Zoom is HIPPA compliant, Partners approved, and the current video software standard for patient care within our Department of Psychiatry.

A member of study staff will mail the accelerometer (ActiGraph, used in Phase II) with detailed instructions on how to use and wear the device after the consent form is received with detailed instructions on how to wear the device and when to start and stop wearing the device. Participants will be provided with a return shipping label and packaging. All participants will wear an accelerometer for 7 days before the first treatment session (baseline) and for 7 days after the final treatment session (post-test).

Next, participants will be emailed links to complete several baseline questionnaires via REDCap. If requested by the participant, questionnaires will be administered by trained research assistants over Zoom using the screen-sharing tool. The research assistant will be responsible for scheduling a participant-preferred time to complete the REDCap questionnaire over Zoom. Participants will be advised they must complete the REDCap survey within one week to ensure that the assessment accurately captures their current functioning. Study staff will call participants up to three times if the participant has not completed the questionnaires 3 days before the due date. Upon completion of the questionnaires, a trained member of study staff will set up a Zoom meeting for the completion of the MoCA, in which the participant will be asked to have a piece of paper and pen or pencil ready before the meeting to display on screen, then the member of study staff will ask the participant to hold up the paper, without their face in frame and take a screenshot of the completed assessment. After completion of the MoCA, a member of study staff will assist the participant with downloading the 6-minute walk test (6MWT) application *(Timed Walk)* on their smart phone that the participant will complete on their own, or with a caregiver and by the requested date from the member of study staff. The *Timed Walk* application, used here for the 6MWT, available on iOS and Android devices has shown to be a valid measure of physical function and a reliable alternative to in-person assessments. Participants will be informed during the consent process and again during the downloading process of this application with a member of study staff that the application will retrieve both GPS location and number of steps taken while completing the assessment. Participants will be told not to save their walk history on the application to maintain privacy and will be asked to instead screenshot or write down the number of steps taken as told by the application to then inform study staff. Study staff will inform participants that they do not have to use the application again until post-test, at which after post-test is complete they may delete the application.

The same procedures for the baseline assessments (accelerometer and REDCap) will be repeated for the post-testing.

Once questionnaires, MoCA, and the 6MWT have been completed, participants will be assigned to one of the two groups using a randomized block design (in blocks of 12 via *sealedenvelope.com*), to ensure that equal numbers of patients are split into the *Active Brains-Fitbit* or the HEP groups. Participants will be notified via email which group they have been assigned to. They will be told that they can participate in one of 2 programs, Active Brains 1 (which is the active intervention) or Active Brains 2 (which is the control group). If participants are assigned to the *Active Brains-Fitbit* group, a study staff will mail a Fitbit device with instructions to the participants. Participants will not be expected to pay for the device or any shipping costs.

One week prior to the start of the group, a research assistant will email all participants to begin wearing the accelerometer device. The research assistant will check-in with all participants via Zoom or phone the same day in order to ensure that there are no technological problems, as well as confirm that all participants are wearing the device properly. The study staff will continue to check in with participants throughout the one-week wear period to ensure adherence. After the one-week period, participants will be asked to return the ActiGraph device using the pre-paid shipping label and packaging provided. Participants will be asked to confirm that they have returned the device via mail. Following the one-week ActiGraph period,

all participants in the *Active Brains-Fitbit* group will pair their FitBit DMD to a smartphone with Bluetooth. A research assistant will schedule a time with all participants to provide guidance via Zoom on how to sync their Fitbit device to their personal phone. Participants in the *Active Brains-Fitbit* group will begin wearing their device for the duration of the program once the device is synced to the participant's phone.

The groups will be conducted virtually by a trained study therapist via Zoom over 10 weeks, which includes 8 group sessions and 2 assessment sessions. Each session will last approximately 90 minutes. Participants can attend the online group sessions from your own home or any other private place with a personal computer. The personal computer must be equipped with a webcam and Zoom videoconferencing software. If needed, members of the research team will contact participants by phone to assist with study-related tasks (e.g., provide technical support to facilitate use of technology). Participants will be invited to participate in an optional focus group exit interview one week after participants have completed the post-test assessments.

In *Active Brains-Fitbit*, participants learn (1) walking skills to gradually average increase through SMART goal-setting, individualized non-pain contingent quota-based pacing (e.g., walk for 30 minutes or meet a step goal of 5,000 steps), and engagement in meaningful activities; (2) mind–body skills to reduce reactivity and catastrophizing to pain or fear of cognitive decline through diaphragmatic breathing body scanning and mindfulness exercises; (3) pain–cognition awareness skills to correct misconceptions about chronic pain and MCI/MRP that may impede participation and understand the disability spiral (e.g., how sedentariness perpetuates chronic pain and MCI/MRP); (4) cognitive functioning skills to develop cognitive compensatory strategies and increase intellectual stimulation; and (5) social and emotional functioning skills to manage negative reactions from others and cope with stress or walking setbacks (positivity, self-compassion, and gratitude). Subjects will be encouraged to complete their homework (logs for mind-body practice, physical activities, and gratitude) each day.

Time-Matched Attention Placebo Active Comparison Condition: Health Enhancement Program (HEP). The active comparison condition controls for the effect of "time spent", "group member support/feedback" and "interventionist support/feedback" and includes delivery of educational information on MCI/MRP and chronic pain symptoms drawn from reputable websites, and standard healthy living information drawn from the Center for Disease Control recommendations and standards for health promotion (e.g., "Sleep", "Nutrition", "Healthy Weight", and "Medical appointments"). Such control interventions are routinely used in stringent RCTs of psychosocial interventions. The HEP program consists on 8 group sessions (each session is 90 minutes) that occur concurrently with the active intervention condition, *Active Brains-Fitbit*. The active comparison HEP is conducted in the same format as the intervention condition but does not include any relaxation response, cognitive behavioral or positive psychology skills training that are reflected in the *Active Brains-Fitbit*. Patients in the HEP receive the same attention from the study therapist as those in the *Active Brains-Fitbit*.

To prevent participant unblinding, participants will be asked not to share specific information discussed in the group (e.g., skills learned, topics discussed) on social media sites (e.g., Facebook groups or internet chat groups) or with other acquaintances for the duration of the study.

During enrollment, participants have the option to consent to receiving reminders in the form of phone calls, text messages, or email over the course of the intervention, depending on personal preference. Participants will be informed of texting risks and provide consent for text messaging in writing or verbally if preferred. Participants will have the opportunity to ask questions about texting with study staff. Approval of text messaging and/or opting out of text messaging will be recorded in each participants file. Between session contact will focus on increasing treatment adherence, maintaining engagement, and session reminders. Text messages will be sent once or twice a week for the duration of the study. Participants may opt-out of the text message contact option at any point.

Participants will be compensated $30 for each assessment completed, and $10 for each session and homework handed in. Participants will also have the option to participate in one exit interview for up to $30. Participants may earn up to $170.

V. BIOSTATISTIC ANALYSIS

Phase I:

The qualitative focus group data and individual exit interview data will be transcribed and analyzed, using NVivo 10 qualitative software, and we will conduct thematic content analysis using guidelines provided by Miles and Huberman (1984). The 2 coders (AMV and study clinician) will meet on an ongoing basis with Dr. Park to discuss the structural thematic

framework, categories, and coding plan. To ensure coding reliability, coding discrepancies will be resolved through discussion and comparison of raw data. Coding will continue until a high reliability (Kappa= >0.80) is established. Once these data analyses are completed, the multidisciplinary team will provide the expert review of data, to discuss the interpretation of our findings in the context of current research on chronic heterogeneous pain.

Phase II/Phase III:

The *Active Brains-Fitbit* group will use a Fitbit DMD through which participants will use Fitbit accounts with deidentified physical measurements (i.e. height and weight) and profile information with approximate birthdays (e.g. month and year only). Participant account names will be set up with "Participant" as the first name and study ID # as the last name. De-identified DMD data will be processed securely through the Fitbit data collection company, Fitabase. Fitabase does not store identifiable data and all participant data is uploaded through encrypted server communication and stored in a highly secure unfractured. Dr. Vranceanu has used Fitabase in previous mind-body intervention studies, including in the current NCCIH R34. The qualitative interview data will be transcribed and analyzed, using NVivo 10 qualitative software, and we will conduct thematic content analysis using guidelines provided by Miles and Huberman (1984). Coders will meet on an ongoing basis with Dr. Vranceanu to discuss the structural thematic framework, categories, and coding plan. To ensure coding reliability, coding discrepancies will be resolved through discussion and comparison of raw data. Coding will continue until a high reliability (Kappa= >0.80) is established. Once these data analyses are completed, the multidisciplinary team will provide the expert review of data, to discuss the interpretation of our findings in the context of current research on chronic pain, MCI, and MRP.

VII. RISKS AND DISCOMFORTS

Patients will be informed that there are no foreseeable physical risks from this research study. They will be informed that in the unlikely situation that they might feel uncomfortable with the topic of discussing within the group, they can alert the group leader who will provide help, as needed. The group leaders are experienced clinical psychologists. They will also be informed that they may feel uncomfortable completing various psychological questionnaires and that they may find it time-consuming to participate in weekly 90-minute groups.

POTENTIAL BENEFITS

Patients will be informed that there may be no direct benefit from participating in this research study. Some patients in the intervention condition of Phase III (*Active Brains-Fitbit*) may become more physically active, more resilient, better able to cope with pain and stress, and experience a better quality of life.

In the future, knowledge from this research may benefit others by providing information on how to better mind body interventions for patients with chronic pain and mild cognitive impairment **or** memory-related problems.

VIII. MONITORING AND QUALITY ASSURANCE

Phase I:
The focus groups will be conducted uniformly using a semi structured interview script that will be finalized during the first few months of the study. The Principal Investigator will be responsible for ensuring compliance with IRB procedures.

Phase II/Phase III:

Electronic information will be stored in REDCap (Research Electronic Data Capture), a free, secure, and HIPAA-compliant web-based application hosted by the Partners HealthCare Research Computing Enterprise Research Infrastructure & Services (ERIS) group (based at the PHS Needham corporate datacenter). Data will be stored on password protected computers that will be stored in secure locations at all times. If any paper data files are used (with coded subject identification) will be stored in a locked filing cabinet. Only research staff will have access to these data locations.

A unique anonymous identifier will be assigned to each subject; subsequently, all data collected will be associated exclusively with this identifier. This includes all questionnaires administered over the course of the study, as well as home practice logs. Data from this study will be stored for three years after the publication of all study results, at which time all paper data files will be shredded and computer files will be deleted.

The group sessions will be conducted using a structured patient manual. The exit interviews will be conducted using a semi-structured interview script in Phase II and will use an unstructured exit interview format to solicit diverse feedback in Phase III. Once completed, a member of study staff will verify that all items on all questionnaires have been addressed. Data will be checked for our of range values using frequency distributions prior to analyzing the data. The PI will be responsible for ensuring compliance with IRB procedures.

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