Title

Four-Week Mentalizing Imagery Therapy for Family Dementia Caregivers: A Randomized Controlled Trial with Neural Circuit Changes

Journal

Psychotherapy and Psychosomatics, 91(3)

ISSN

0033-3190

Authors

Jain, Felipe A
Chernyak, Sergey V
Nickerson, Lisa D
et al.

Publication Date

2022

DOI

10.1159/000521950

Peer reviewed

HHS Public Access

Author manuscript

Psychother Psychosom. Author manuscript; available in PMC 2023 March 14.

Published in final edited form as:

Psychother Psychosom. 2022 ; 91(3): 180–189. doi:10.1159/000521950.

4-week Mentalizing Imagery Therapy for family dementia caregivers: A randomized controlled trial with neural circuit changes

Felipe A. Jain, M.D.[a], **Sergey V. Chernyak, Ph.D.**[a], **Lisa D. Nickerson, Ph.D.**[b], **Stefana Morgan, M.D., Ph.D.**[c], **Rhiana Schafer, B.S.**[d], **David Mischoulon, M.D., Ph.D.**[a], **Richard Bernard-Negron, B.S.**[a], **Maren Nyer, Ph.D.**[a], **Cristina Cusin, M.D.**[a], **Liliana Ramirez Gomez, M.D.**[e], **Albert Yeung, M.D.**[a]

[a]Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[b]Applied Neuroimaging Statistics Laboratory, McLean Hospital, Harvard Medical School, Belmont, MA, USA

[c]Weill Institute for Neurosciences and Langley Porter Psychiatric Hospital and Clinics, University of California, San Francisco, CA, USA

[d]Department of Neurology, Northwestern University, Chicago, IL, USA

[e]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Abstract

Introduction—Family caregivers of patients with dementia suffer a high burden of depression and reduced positive emotions. Mentalizing Imagery Therapy (MIT) provides mindfulness and guided imagery skills training to improve balanced mentalizing and emotion regulation.

Objective—To test the hypotheses that MIT for family caregivers would reduce depression symptoms and improve positive psychological traits more than a support group (SG), and would increase dorsolateral prefrontal cortex (DLPFC) connectivity and reduce subgenual anterior cingulate cortex (sgACC) connectivity.

Corresponding Author: Felipe A. Jain, MD, Department of Psychiatry, Depression Clinical and Research Program, Massachusetts General Hospital, Harvard Medical School, One Bowdoin Square, 6th Floor, Boston, MA 02114, USA, Tel: +1-617-643-4682, felipe.jain@post.harvard.edu.

Author Contributions

Felipe A. Jain, M.D. designed and conducted the trial, analyzed the data, drafted the manuscript, and approved the final version of the manuscript.

Sergey V. Chernyak, Ph.D., analyzed the data, edited the manuscript, and approved the final version of the manuscript.

Lisa D. Nickerson, Ph.D., assisted with design of the data analysis, edited the manuscript, and approved the final version of the manuscript.

Stefana Morgan, M.D., Ph.D., participated in data collection, edited the manuscript, and approved the final version of the manuscript.

Rhiana Schafer, B.S., participated in data collection, edited the manuscript, and approved the final version of the manuscript.

Statement of Ethics

Study approval statement: The study was approved by the Human Subjects Protection Committee of the University of California, San Francisco (UCSF) #16–20163 and Massachusetts General Hospital #2018P000798.

Consent to participate statement: Written informed consent was obtained from participants to participate in the study.

Methods—46 caregivers participated in a randomized controlled trial comparing a 4-week MIT group (n=24) versus SG (n=22). Resting state neuroimaging was obtained at baseline and post group in 28 caregivers, and questionnaires completed by all participants. Primary outcome was change in depression; secondary measures included anxiety, mindfulness, self-compassion and well-being. Brain networks with participation of DLPFC and sgACC were identified. Connectivity strengths of DLPFC and sgACC with respective networks were determined with dual regression. DLPFC-network connectivity was correlated with depression outcome.

Results—MIT significantly outperformed SG in improving depression, anxiety, mindfulness, self-compassion, and well-being, with moderate to large effect sizes. Relative to SG, participants in MIT showed significant increases in DLPFC connectivity – exactly replicating pilot study results – but no change in sgACC. DLPFC connectivity change correlated positively with mindfulness and negatively with depression change.

Conclusions—In this trial, MIT was superior to SG for reducing depression and anxiety symptoms and improving positive psychological traits. Neuroimaging results suggested that strengthening DLPFC connectivity with an emotion regulation network might be mechanistically related to MIT effects.

Keywords

mindfulness; mentalization; family caregivers; neuroimaging; depression

Introduction

The needs of caregivers of family members with chronic mental illness including major neurocognitive disorder (dementia) are often overlooked by health professionals, who are taught to focus their efforts on symptomatic management of the patient. Caregivers, who are often “invisible second patients” [1], exhibit high rates of syndromal and subsyndromal depression and anxiety, as well as physical comorbidities related to chronic stress [2]. Institutionalization of the care recipient is more likely to occur in the setting of high caregiver emotional stress and burden [3]. There is a great need to identify robust strategies for caregivers that may rapidly improve psychological symptoms and well-being.

Caregivers of patients with mental disorders such as dementia struggle with attempting to understand (mentalize) a mind that deviates markedly from their own. Cognitive deterioration can result in unfamiliar patterns of behavior and cognition such that caregivers feel they are “becoming strangers” with the relative living with dementia [4]. Caregivers also struggle with shame and guilt regarding their own reactions and behaviors under chronic stress, and have difficulty understanding ambiguous or unsupportive responses of family members and friends.

Mentalizing Imagery Therapy (MIT) combines principles of mentalization – which has been postulated as a common mechanism of action of effective psychotherapies [5] – with guided imagery and mindfulness skills training [6]. Whereas “first-generation” mindfulness therapies in clinical practice mostly focus on internal sensations of the self during the controlled meditation practice (or nonjudgmental sensory experiencing when acting) [7],

MIT switches between mindful attention to images of self and other, including emotional reactions to challenging situations from different perspectives, in an attempt to achieve balanced mentalizing [6]. MIT further focuses the participant on their connectedness to communities and their larger natural environment to help reduce emotional arousal and thereby facilitate mentalizing capacity [8] and improve depressive and anxious symptoms [9].

Changes in behavioral and mental symptoms may in part be underpinned by changes in connectivity of functional brain networks in which individual brain regions serve as nodes that perform specific functions. Two brain regions frequently associated with depression and regulation of low mood are the dorsolateral prefrontal cortex (DLPFC) and the subgenual anterior cingulate cortex (sgACC). The DLPFC is an important region for cognitive and emotional regulation, with involvement in planning, attention, and regulation of emotional and behavioral responses [10]. A pilot trial found that MIT was associated with increased connectivity of DLPFC with an emotion regulation network [9]. sgACC activity has been associated with experiences of sadness, and abnormal connectivity of sgACC to downstream targets such as the nucleus accumbens and amygdala has been hypothesized as a mechanism of Major Depressive Disorder [11].

To test the hypothesis that MIT would be beneficial for reducing negative psychological symptoms and improving positive traits in family caregivers of dementia patients, we conducted a randomized, controlled trial of MIT versus a psychoeducational support group (SG) with a primary outcome of self-reported depression symptoms. We hypothesized that increased connectivity of the DLPFC with the emotion regulation network (as observed in our pilot trial), and reducted connectivity of the sgACC with a ventral emotion processing network (including nucleus accumbens and amygdala), would be associated with MIT relative to SG. We further hypothesized that increased DLPFC connectivity would be associated with reduction in depression symptoms and improvements in trait mindfulness.

Materials and Methods

The study was approved by the Human Subjects Protection Committee of the University of California, San Francisco (UCSF) and Massachusetts General Hospital. The clinical trial was pre-registered at clinicaltrials.gov (#NCT03092050). Subjects were recruited from 2017 to 2019 with posted flyers, Facebook advertisements and direct mail or phone calls to caregivers of known dementia patients at UCSF. Subjects were screened by telephone to determine preliminary eligibility and describe group and assessment procedures, and this was followed by an in-person interview to confirm eligibility and explain study procedures, followed by written informed consent.

Participants were required to identify as the primary family caregiver for a loved one with dementia, at least 40 years of age and fluent in written and oral English. Initially, there was a requirement that participants score at least 10 on the Patient Health Questionnaire (PHQ)-9 (moderate depression symptoms); however, after the first 100 prospective participants were screened, this requirement was eliminated to improve generalizability to the broader caregiver population interested in the study. Participants who had initially failed the

screening interview based on this criterion were re-contacted to determine interest in participation.

Exclusion criteria included primary psychiatric disorder other than unipolar depression, unstable medical illness or planned surgery interfering with participation, violence or intent to harm relative with dementia, open Adult Protective Services report on file, caregiver cognitive impairment, or meditation/imagery practice more than twice a week. Please refer to Figure 1 for CONSORT flow diagram.

Randomization and blinding

A group randomization scheme was generated from random.org. Baseline assessments were completed and after 6–8 subjects were recruited (dependent on volume of calls received within an acceptable time interval), participants were informed of randomization assignments and a group was scheduled. Participants were blinded to study hypotheses but not to group, and all participants were informed that the investigators expected that both interventions would be helpful. Participants were also informed they would be eligible to receive the intervention to which they were not initially assigned, after their four-month assessment.

Group Treatment

Treatment groups consisted of four weekly 120-minute sessions followed by optional "refreshers" at 1 and 2 months post initial group completion. As previously described [9], the MIT group provided weekly mindfulness exercises including low-impact stretching and breath focused meditation, as well as specific guided imagery exercises that changed week to week, designed to elicit attention to various aspects of mentalizing (self-other, automatic-controlled, internal-external, emotion-cognition) and to help situate the caregiver in their connectedness with a larger social and ecological context [6]. Each support group (SG) consisted of facilitated discussions focusing on challenges each caregiver faced, preceded by brief (about 20 minutes) psychoeducational topics related to caregiving (Online Supplementary Material, OSM).

Questionnaires

For the primary outcome, the Quick Inventory of Depression Symptomatology – Self Report (QIDS-SR) [12] was administered at baseline, post group (about 4 weeks after the first group session), and 4 months with REDCAP software, and collected prior to each group session using a written questionnaire. For secondary outcomes, questionnaires were administered at baseline, post group, and at 4 months. The clinician-rated Hamilton Depression Rating Scale – 17 item (HAMD) [13,14] was conducted by semi-structured interview by a clinician with more than 5 years of experience and training in this scale and is known to be a sensitive and valid instrument for the measurement of depressive symptoms and symptom change [15]. Additional self-rated questionnaires included the Acceptance and Action Questionnaire II [16], Five Factor Mindfulness Questionnaire (FFMQ) for trait mindfulness [17], Mental Health Continuum (MHC) for perceived well-being [18], Positive and Negative Affect Scale (PANAS) [19], Self Compassion Scale – Short Form [20], State Trait Anxiety Inventory (STAI) [21], Zarit Caregiver Burden Scale (CBS) [22]. Expectancy

measures were modified from Borkovec and Nau [23] (OSM). Home practice logs were provided to MIT participants to document their mindfulness and guided imagery sessions during the 4-week group (OSM). Measures were selected consistent with principles of incremental validity for clinical trials [24].

MRI preprocessing

Pre-processing was performed with *fMRIPprep* 1.2.6 [25]. Of 31 participants scanned, 1 dataset was discarded due to poor image quality, and 2 datasets were excluded due to excessive motion, resulting in complete MRI data for N=15 in MIT and N=13 in SG. Group ICA was performed using FSL MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) Version 3.09 [26], to implement a data-driven functional parcellation of the brain for hypothesis testing [27]. Dual regression was employed to obtain the subject-level spatial connectivity maps, corresponding to each group independent component that represented a resting-state network of interest [28]. Networks were visually inspected to identify those with bilateral DLPFC and sgACC as major nodes of the network and selected on the basis of pilot data. The average regression weights were computed for the DLPFC and sgACC regions with their respective networks, and these weights were used for statistical analyses (OSM).

Statistical analysis

Clinical measures.—All analyses were performed with R 3.5.1 [29]. Outcomes on the intention to treat sample were assessed with linear mixed models (lme), with Time and Group × Time as fixed factors and Participant as a random factor, and Age and Sex as covariates. Because participants were randomly assigned, we retained the baseline in the dependent variable, and a separate main effect of group was not included in the model [30]. If visual inspection of residuals suggested deviation from normality, a square root transform was applied and normality of residuals from the resulting model was confirmed. The pre-specified primary outcome was QIDS-SR change from baseline to post group (about 4 weeks after the first group session). For the QIDS-SR scores obtained (in writing) at each group, questionnaires were discarded if more than 2 items were left blank (<2% of questionnaires). If 1 or 2 items were missing (<3% of questionnaires), mean imputation was performed for the missing values. Secondary outcomes included change in all other clinical measures from baseline to post group and 4-month follow-up. With a sample size of 46, we had 80% power to detect an effect size of $f = .21$ (a small effect) with alpha = .05 using our repeated measures design and with an *a priori* post-group timepoint selected for the primary outcome. To analyze rapid mood change from before to after meditation practice, we implemented a mixed effects model with mood rating as the dependent variable, a binary fixed effect for before/after meditation, and a random factor for subject.

The number of patients with deterioration of depressive symptoms from baseline to the post-group or 4-month assessments was examined according to recommended practices for the reporting of psychotherapy trials [31]. Deterioration was defined sensitively as an increase of at least 3 points on the QIDS-SR or an increase of at least 4 points HAMD, with thresholds chosen due to potential clinical meaningfulness of these changes [32,33]. Difference in deterioration between groups was assessed with the Fisher exact test [34].

Neuroimaging analyses.—To determine differences in dlPFC and sgACC connectivity with their respective networks between groups, data were inspected for normality, square root transform applied as appropriate, and two-sided unpaired t-tests performed as per our pilot work [9]. Significance was considered to be at p=.025 to Bonferroni correct for two comparisons. Follow up within group comparisons were made with two-sided paired t-tests. Partial correlations of DLPFC within-network connectivity change with self- and clinician-rated depression symptom change and mindfulness change were obtained across groups in R using package ppcor [35]. Covariates including baseline connectivity, baseline depression symptoms, group, age and sex, and significance was set at p=.0167 to correct for three comparisons. Partial correlations were also examined separately within group to determine whether they were in the same direction and with similar magnitude [36].

Results

Demographic and clinical sample

Caregivers were on average older adult and female (Table 1). They were generally college educated and had been caring for their relative for several years. Approximately 1/3 suffered from a current major depressive episode. There were no significant differences among groups in baseline demographic or clinical characteristics in any of the measures assessed (Table 1).

Expectancy

There were no differences between groups in baseline expectancy measures such as logic of the treatment, confidence, recommendation or applicability, nor were there Group × Time differences. Depression symptom change (self or clinician rated) was not associated with baseline or change in expectancy measures for either group (p>.1 for all comparisons).

Attendance and home meditation practice

Caregivers attended on average 3±1 (SD) sessions in both groups, across participants 80/96 (83%) sessions of MIT and 71/84 (85%) sessions of SG. Caregivers in the MIT group practiced meditation and guided imagery exercises at home on average 5±3 (SD) times a week, for 18±5 minutes each session. “Overall feeling state” improved rapidly from before to after meditation by 2.5±2.4 points on the Likert scale across all MIT sessions, $p<10^{-10}$ (OSM Figure). Refresher session attendance was similar among completers of both groups: 71% of MIT and 62% of SG attended at least one session, and 25% of MIT and 19% of SG attended both.

Depression symptoms

The pre-specified primary endpoint, reduction in QIDS-SR, was met (mean [95% CI], MIT −3.4 [−5.0, −1.8], and SG −1.0 [−2.7, 0.3], Table 2), p=.02. Review of weekly symptomatic change suggested that while both groups were associated with early reduction in depression symptoms, only the MIT group experienced durable improvements post-group and at the four-month follow up (shown in Fig. 2). HAMD was also reduced post-group in MIT relative to SG, (MIT −5.5 [−7.8, −3.5], and SG −0.4 [−2.7, 1.9], p=.0002. Effect sizes were

comparable at 4 months in the MIT group relative to SG (Table 2). Please refer to the OSM for a case study of MIT illustrating these benefits in a single study participant.

Deterioration of depressive symptoms was observed in 6 participants (29%) in SG and no participants in MIT at the post-group assessment (p=.001). Between baseline and 4 months, 7 participants (33%) in SG and 1 participant (4%) in MIT evinced deterioration (p=.02).

Secondary negative psychological symptom outcomes

The MIT group exhibited a greater reduction in anxiety than SG. Both interventions were associated with improvements in caregiver burden and negative affect, without significant differences between groups (Table 2).

Positive Psychological outcomes

Caregivers in the MIT arm exhibited significantly increased trait mindfulness, well-being, acceptance and self-compassion relative to those in SG at post-group and follow-up (Table 2).

Dorsolateral prefrontal cortex connectivity

Group differences.—The DLPFC network principally included bilateral DLPFC, DMPFC, VLPFC and cognitive-affective regions of the cerebellum (OSM). There were no differences in baseline DLPFC connectivity between groups (2.38±2.08 for MIT vs 2.89±2.25 for SG, p=.51. Increase in within network DLPFC connectivity was observed in the MIT group relative to SG (1.75 [.73, 2.77] for MIT vs −.53 [−1.88, .82] for SG, p=.019). The MIT group demonstrated a highly significant within group DLPFC connectivity change (p=.002); whereas SG showed no change (p=.6).

Partial correlations with symptom change.—Combining both groups, DLPFC connectivity change correlated with change in HAMD (r= −.41, p=.015) and trait mindfulness (r=.69, p=.0003), but not QIDS-SR (r= −.40, p=.04). Review of correlation coefficients within each group showed similar magnitude and direction of change (not shown).

Subgenual anterior cingulate connectivity

There were no differences in sgACC-network connectivity at baseline (p=.2), nor within (p≥.2 in both groups) or between group connectivity changes (p=.09) (OSM). Because there were no group differences, partial correlations for changes in sgACC-network connectivity with changes in symptoms were not explored.

Discussion/Conclusion

In this pilot randomized controlled trial of MIT for family dementia caregivers, MIT demonstrated improvements relative to a highly active control support group in both depression and anxiety symptoms and positive psychological traits, including rapidly within the caregivers' ecological setting after home practice and over the 4-month follow-up period. While both groups evidenced benefit in negative and positive affective domains, MIT was

superior on the primary outcome of self-rated depression symptoms and several secondary outcomes. The benefits of MIT were stable or increased at 4 months, when many of the SG's benefits had begun to fade. Moreover, neuroimaging findings of increased DLPFC-network connectivity were consistent with clinical findings and a large body of evidence suggesting these modulations reduce depression [37].

The proportion of caregivers showing deterioration of depressive symptoms in SG was approximately one-third of the sample at each follow up timepoint, which was significantly higher than for those receiving MIT. While the uncertainty of the size of effect is unclear due to limitations of the sample size, these findings indicate a high vulnerability in this population to depressive symptoms without effective treatment. Although depressive symptoms for participants in SG on average improved, there is a significant proportion for whom the environment of SG was unhelpful or might even have been experienced as aversive. Future studies should examine reasons for deterioration using mixed methods approaches. Caregivers in clinical trials should be closely monitored, and those who deteriorate (or do not improve) should receive follow up with additional psychotherapeutic intervention.

Earlier studies of mindfulness-based approaches for family dementia caregivers demonstrated amelioration of negative affective symptoms, but have not generally reported on positive psychological traits [38]. This study showed a lasting improvement associated with MIT relative to SG in multiple positive measures of mental health, including mindfulness, positive mood, acceptance, self-compassion and well-being. Because positive emotions may buffer effects of psychosocial stress and broaden adaptive behaviors [39], we suggest that MIT might contribute to flexible and adaptive social behaviors in caregivers.

Increase in within network DLPFC connectivity in the MIT group versus SG group extend prior work that shows that mindfulness training increases DLPFC connectivity in anxiety [40] and post traumatic stress disorder (PTSD) [41]. The correlation across groups between DLPFC connectivity and reduction in diverse symptoms of generalized anxiety disorder [40], PTSD associated hyperarousal [41], and now depression symptoms suggests that strengthening of DLPFC connectivity with other prefrontal cortical regions may contribute to symptom reduction across diagnoses. Our results differ from those previously reported in that we examined DLPFC connectivity specifically within a putative emotion regulation network consisting of DMPFC and DLPFC. The magnitude of the DLPFC-network connectivity change correlations with both change in depression symptoms and mindfulness was similar between the MIT and SG group, and this raises the possibility that DLPFC connectivity increase represents a common mechanism to clinical improvement across both psychotherapies – one which MIT engaged more strongly.

Within group strengthening of DLPFC connectivity with the emotion regulation network exactly replicates DLPFC-network increase with MIT shown in our pilot trial, which analyzed the identical DLPFC region of interest and network [9]. This replication is despite the fact that data from the pilot trial were obtained on different MRI scanners, with different scanning parameters, and at a different institution (University of California, Los Angeles). These results provide among the first exact replications of a brain connectivity biomarker

associated with psychotherapy treatment. The robustness of these findings despite small sample sizes and different protocols increases confidence in our results. Contrary to our hypothesis and pilot data, we did not observe significant reduction in sgACC connectivity with a network comprised principally of amygdala and nucleus accumbens. The lack of sgACC-network connectivity change might indicate that MIT does not directly target emotion salience or reward related processes [42], but this hypothesis should be directly tested.

Limitations of our study included the small sample size, which may have resulted in Type II error that precluded us from observing statistically superior benefits of MIT on outcome variables such as caregiver burden, whose effect size favored MIT. Second, the clinician evaluating depression symptoms was not blind to treatment assignment. However, self-rated depression symptoms at baseline, post group and follow up were obtained using a computerized entry and record system without the investigators present. Moreover, neither clinician-rated nor self-rated depression symptoms showed association with expectancy effects. Although there were no significant baseline demographic differences between groups, there were approximately double the number of men in SG and MIT and a moderate effect size for age to be higher in SG. We therefore used covariates of sex and age in clinical outcome models, and believe that further trials with larger and more comparable samples are warranted. Finally, we should not infer that MIT is superior to community-delivered support groups, which are designed as long-term therapeutic options. We speculate that an optimal approach for family caregivers would involve MIT training in conjunction with other therapies including support groups, respite care, targeted biological therapies and other personally tailored assistance, and this should be studied in further research.

Our findings suggest that a short, 4-week course of MIT can result in substantial and lasting psychological benefits for caregivers. As a novel mindfulness and guided imagery therapy that intentionally seeks to balance mentalizing, MIT may fit a unique therapeutic niche for those who suffer from chronic relationship stress. Validation of the findings and verification of utility in clinical practice is needed with larger controlled pragmatic trials. The favorable benefits of MIT for depression and positive psychological traits suggest that it may be studied not only to ameliorate negative affective symptoms, but also to promote recovery and improve subjective well-being.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

We would like to thank Erin Hubbard, MA, and Charissa Hosseini, PhD, for assistance with leading psychotherapy groups; Jonathan Dreyfuss, PhD, and Joseph Locascio, PhD, for expert statistical advice; Sara Lazar, PhD, for helpful comments on the manuscript; and Francis Chen, BA, Abu Sikder, BA, Taquesha Dean, BA, Alexandra Morford, BA, and Nora Huey, BA, for administrative research assistance.

Conflict of Interest Statement

Dr. Felipe Jain has received honoraria for speaking from the Benson Henry Institute for Mind/Body Medicine at the Massachusetts General Hospital, and for serving as a grant reviewer for Fondazione Cariplo. Dr. Albert Yeung

has received financial support from Beijing Hailan Happy Family Culture Co. Ltd. Dr. Liliana Ramirez Gomez has received honoraria from the Massachusetts Neurological Association. Dr. David Mischoulon has received research support from Nordic Naturals and heckel medizintechnik GmbH. He has received honoraria for speaking from the Massachusetts General Hospital Psychiatry Academy. Drs. David Mischoulon, Felipe Jain and Maren Nyer have worked with the non-profit MGH Clinical Trials Network and Institute, which has received research funding from multiple pharmaceutical companies and the National Institute of Mental Health (NIMH). Dr. Cristina Cusin has received grant support from the American Foundation for Suicide Prevention and NIMH. She has received consulting honoraria from Janssen, Takeda, Boehringer, Lundbeck, Alkermes, Clexio and Perception Therapeutics. She has a patent (PCT/US15/56192; 070919.00032) for Acyliccucurbit[N]uril type molecular containers to treat intoxication and substance abuse, and reports royalties from Springer. Drs. Sergey V. Chernyak, Lisa D. Nickerson and Stefana Morgan have no conflicts of interest to declare.

Funding Sources

This work was supported by the National Institute on Aging #R21AG051970, #K76AG064390, and a Jerome and Celia Reich Award in Depression Research (PI - Felipe A. Jain). This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL 1TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers, to Dr. Jonathan Dreyfuss and Dr. Lisa D. Nickerson. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

References

1. Brodaty H, Donkin M. Clinical research: Family caregivers of people with dementia. Dialogues Clin Neurosci. 2009;11(2):217–28. [PubMed: 19585957]
2. Schulz R, Sherwood PR. Physical and Mental Health Effects of Family Caregiving. Am J Nurs. 2008 Sep;108(Supplement):23–7.
3. Gaugler JE, Yu F, Krichbaum K, Wyman JF. Predictors of nursing home admission for persons with dementia. Med Care. 2009;47(2):191–8. [PubMed: 19169120]
4. Wuest J, Ericson PK, Stern PN. Becoming strangers: the changing family caregiving relationship in Alzheimer's disease. J Adv Nurs. 1994 Sep;20(3):437–43. [PubMed: 7963047]
5. Allen J, Fonagy P. Mentalizing in psychotherapy. Am Psychiatr Publ Textb Psychiatry, sixth Ed. 2014 DOI: 10.1176/appi.books.9781585625031.rh31
6. Jain FA, Fonagy P. Mentalizing Imagery Therapy: Theory and Case Series of Imagery and Mindfulness Techniques to Understand Self and Others. Mindfulness (N Y). 2020 Jan;11(1):153–65. [PubMed: 32042350]
7. Van Gordon W, Shonin E. Second-Generation Mindfulness-Based Interventions: Toward More Authentic Mindfulness Practice and Teaching. Mindfulness (N Y). 2020 Jan;11(1):1–4.
8. Yang FC, Zamaria J, Morgan S, Lin E, Leuchter AF, Abrams M, et al. How family dementia caregivers perceive benefits of a 4-week Mentalizing Imagery Therapy Program: a pilot study. Prof Psychol Res Pract (accepted Manuscr Press. 2021
9. Jain FA, Chernyak S, Nickerson L, Abrams M, Iacoboni M, Christov-Moore L, et al. Mentalizing Imagery Therapy for depressed family dementia caregivers: Feasibility, clinical outcomes and brain connectivity changes. J Affect Disord Reports. 2021;5:100155.
10. Dixon ML, Thiruchselvam R, Todd R, Christoff K. Emotion and the prefrontal cortex: An integrative review. Psychol Bull. 2017 Oct;143(10):1033–81. [PubMed: 28616997]
11. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry. 2007;62(5):429–37. [PubMed: 17210143]
12. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003 Sep;54(5):573–83. [PubMed: 12946886]
13. Hamilton M A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62. [PubMed: 14399272]

14. Morriss R, Leese M, Chatwin J, Baldwin D, THREAD Study Group. Inter-rater reliability of the Hamilton Depression Rating Scale as a diagnostic and outcome measure of depression in primary care. J Affect Disord. 2008 Dec;111(2–3):204–13. [PubMed: 18374987]
15. Carrozzino D, Patierno C, Fava GA, Guidi J. The Hamilton Rating Scales for Depression: A Critical Review of Clinimetric Properties of Different Versions. Psychother Psychosom. 2020 Apr;89(3):133–50. [PubMed: 32289809]
16. Bond FW, Hayes SC, Baer RA, Carpenter KM, Guenole N, Orcutt HK, et al. Preliminary Psychometric Properties of the Acceptance and Action Questionnaire – II : A Revised Measure of Psychological Inflexibility and Experiential Avoidance. Behav Ther. 2011;42(4):676–88. [PubMed: 22035996]
17. Baer RA, Smith GT, Lykins E, Button D, Krietemeyer J, Sauer S, et al. Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. Assessment. 2008;15(3):329–42. [PubMed: 18310597]
18. Keyes CLM. The Mental Health Continuum: From Languishing to Flourishing in Life. J Health Soc Behav. 2002 Jun;43(2):207. [PubMed: 12096700]
19. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol. 1988 Jun;54(6):1063–70. [PubMed: 3397865]
20. Raes F, Pommier E, Neff KD, Van Gucht D. Construction and factorial validation of a short form of the Self-Compassion Scale. Clin Psychol Psychother. 2011;18(3):250–5. [PubMed: 21584907]
21. Spielberger CD, Gorsuch RL, Lushene RE. State-trait anxiety inventory. Palo Alto. CA: Consulting Psychologists Press; 1970.
22. O'Rourke N, Tuokko HA. Psychometric properties of an abridged version of The Zarit Burden Interview within a representative Canadian caregiver sample. Gerontologist. 2003 Feb;43(1):121–7. [PubMed: 12604753]
23. Borkovec TD, Nau SD. Credibility of Analogue Therapy Rationales. J Behav Ther Exp Psychiatry. 1972;3(4):257–60.
24. Carrozzino D, Patierno C, Guidi J, Berrocal Montiel C, Cao J, Charlson ME, et al. Clinimetric Criteria for Patient-Reported Outcome Measures. Psychother Psychosom. 2021;90(4):222–32. [PubMed: 34038901]
25. Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A, et al. fMRIPrep: a robust preprocessing pipeline for functional MRI. Nat Methods. 2019 Jan;16(1):111–6. [PubMed: 30532080]
26. Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc B Biol Sci. 2005 May;360(1457):1001–13.
27. Pervaiz U, Vidaurre D, Woolrich MW, Smith SM. Optimising network modelling methods for fMRI. Neuroimage. 2020 May;211. DOI: 10.1016/J.NEUROIMAGE.2020.116604
28. Nickerson LD, Smith SM, Öngür D, Beckmann CF. Using Dual Regression to Investigate Network Shape and Amplitude in Functional Connectivity Analyses. Front Neurosci. 2017 Mar;11:115. [PubMed: 28348512]
29. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018. DOI: 10.1007/978-3-540-74686-7
30. Fitzmaurice G, Laird N, Ware J. Applied Longitudinal Analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2011, pp128–129.
31. Guidi J, Brakemeier E-L, Bockting CL, Cosci F, Cuijpers P, Jarrett RB, et al. Methodological Recommendations for Trials of Psychological Interventions. Psychother Psychosom. 2018 Sep;87(5):276–84. [PubMed: 30007961]
32. Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, et al. The Inventory of Depressive Symptomatology, clinician rating (IDS-C) and self-report (IDS-SR), and the Quick Inventory Depressive Symptomatology, clinician rating (QIDS-C) and self-report (QIDS-SR) in public sector patients with mood disorders: A psychome. Psychol Med. 2004;34(1):73–82. [PubMed: 14971628]

33. Rush AJ, South C, Jain S, Agha R, Zhang M, Shrestha S, et al. Clinically Significant Changes in the 17- and 6-Item Hamilton Rating Scales for Depression: A STAR*D Report. Neuropsychiatr Dis Treat. 2021;17:2333–45. [PubMed: 34295161]
34. Raymond M, Rousset F. An exact test for population differentiation. Evol Int J Org Evol. 1995;49(6):1280–3.
35. Kim S ppcor: An R Package for a Fast Calculation to Semi-partial Correlation Coefficients. Commun Stat Appl Methods. 2015 Nov;22(6):665–74. [PubMed: 26688802]
36. Kievit RA, Frankenhuis WE, Waldorp LJ, Borsboom D. Simpson's paradox in psychological science: A practical guide. Front Psychol. 2013;4(AUG). DOI: 10.3389/fpsyg.2013.00513
37. Fonseka TM, MacQueen GM, Kennedy SH. Neuroimaging biomarkers as predictors of treatment outcome in Major Depressive Disorder. J Affect Disord. 2018 Jun;233:21–35. [PubMed: 29150145]
38. Liu Z, Chen Q-L, Sun Y-Y. Mindfulness training for psychological stress in family caregivers of persons with dementia: a systematic review and meta-analysis of randomized controlled trials. Clin Interv Aging. 2017 Sep;12:1521–9. [PubMed: 29026290]
39. Fredrickson BL. The role of positive emotions in positive psychology. The broaden-and-build theory of positive emotions. Am Psychol. 2001 Mar;56(3):218–26. [PubMed: 11315248]
40. Holzel BK, Hoge EA, Greve DN, Gard T, Creswell JD, Brown KW, et al. Neural mechanisms of symptom improvements in generalized anxiety disorder following mindfulness training. Neuroimage Clin. 2013;2:448–58. [PubMed: 24179799]
41. King AP, Block SR, Sripada RK, Rauch S, Giardino N, Favorite T, et al. Altered default mode network (DMN) resting state functional connectivity following a mindfulness-based exposure therapy for posttraumatic stress disorder (PTSD) in combat veterans of Afghanistan and Iraq. Depress Anxiety. 2016 Apr;33(4):289–99. [PubMed: 27038410]
42. Hamani C, Mayberg H, Stone S, Laxton A, Haber S, Lozano AM. The subcallosal cingulate gyrus in the context of major depression. Biol Psychiatry. 2011 Feb;69(4):301–8. [PubMed: 21145043]

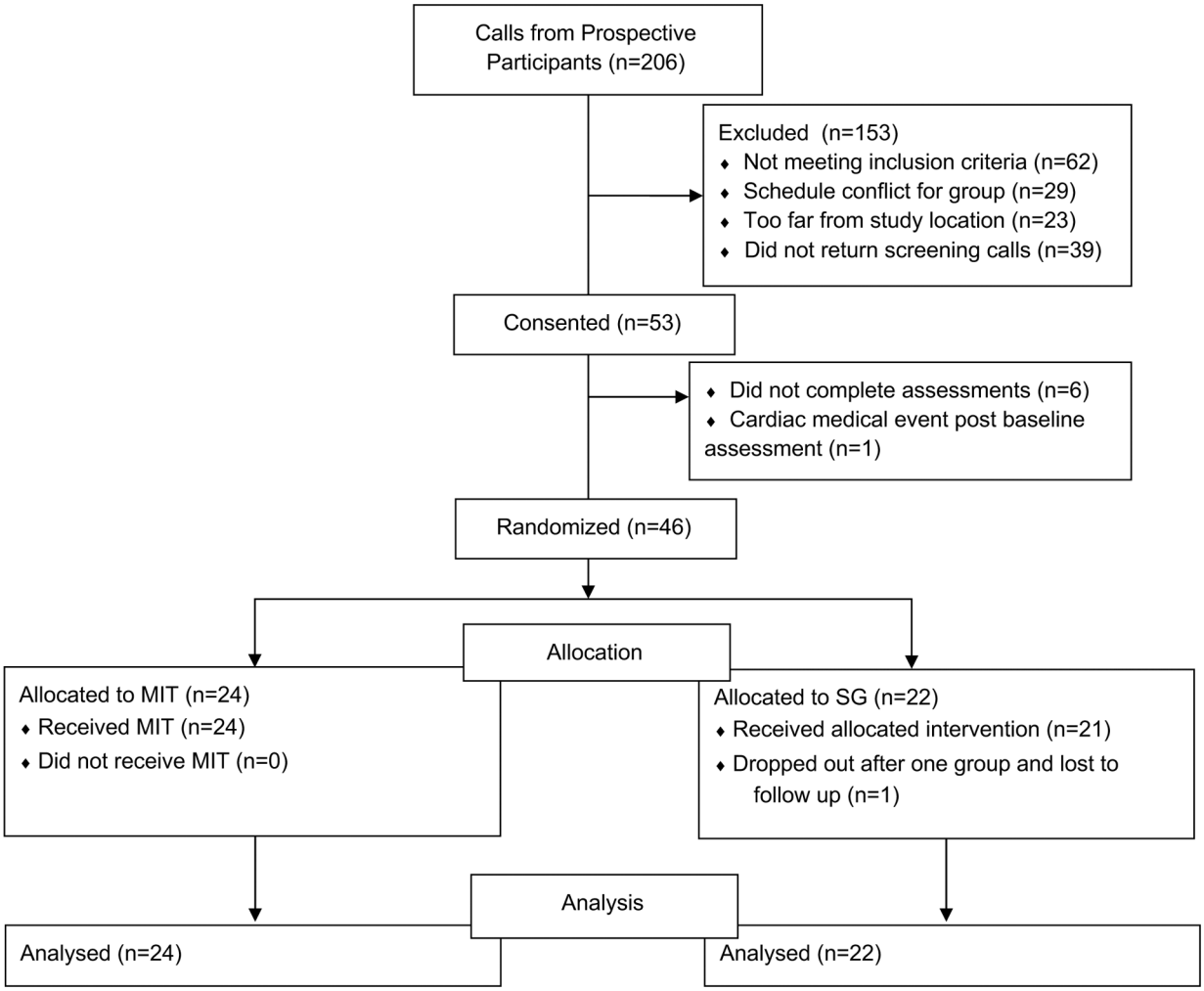

Fig 1.
CONSORT flow diagram. MIT = Mentalizing Imagery Therapy, SG = Support Group.

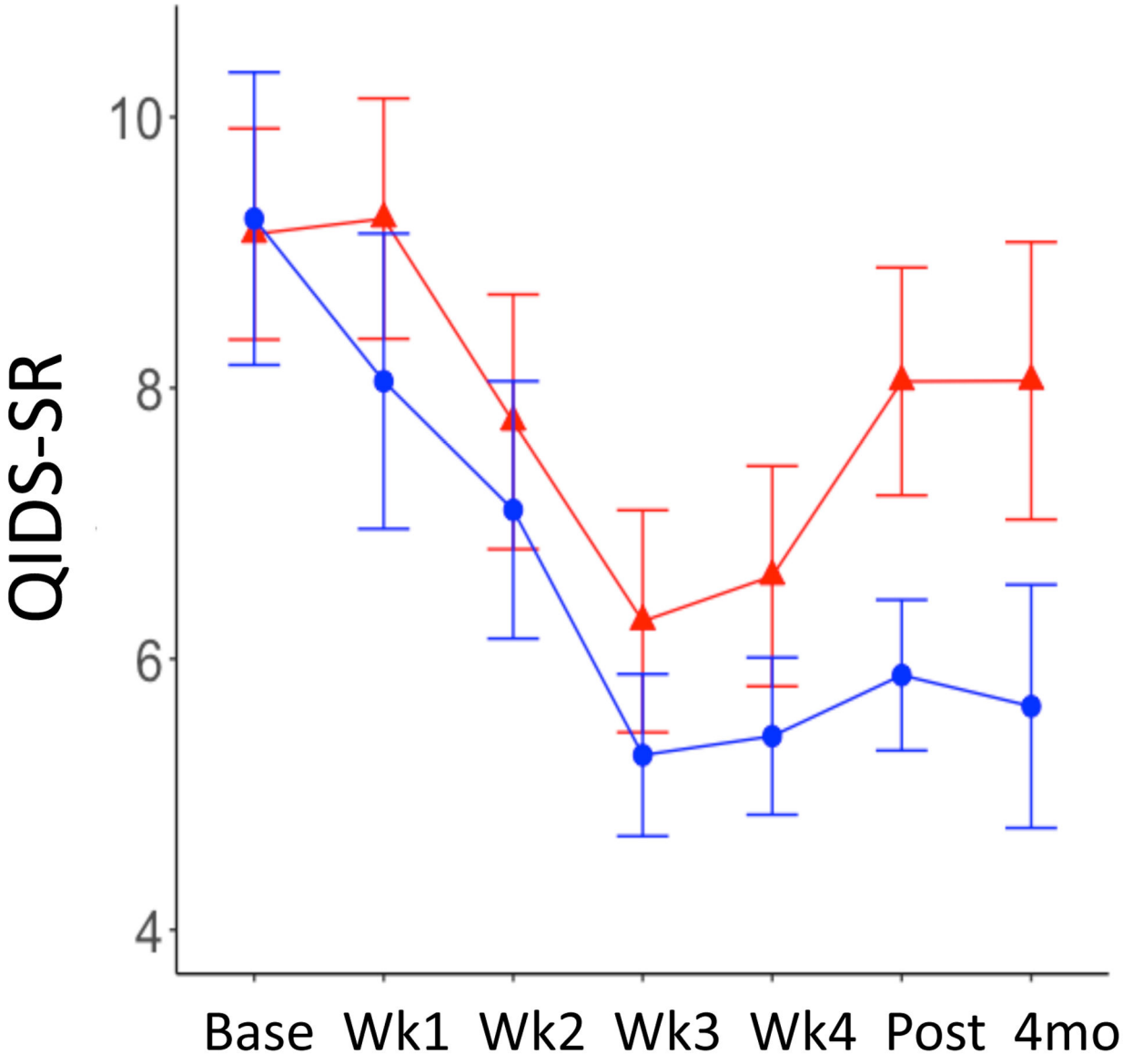

Fig 2.

Primary outcome self-rated depression. MIT = Blue circles and line; SG = red triangles and line; errorbars indicate one standard error from the mean; Base=baseline; Post = post group visit; QIDS-SR = Quick Inventory of Depression Symptoms – Self Report; Wk = week of group therapy session; 4mo = 4 month follow up

Table 1.

Demographic, caregiving and clinical characteristics of participants at baseline

	Mentalizing Imagery Therapy (n=24)	Support Group (n=22)	*p* value
Age, mean (SD) [range], y	61.0 (8.4) [46 – 77]	66.1 (9.8) [46 – 85]	.07
Sex, female, N (%)	21 (87.5)	16 (72.7)	.16
Race, N (%)			
White/Caucasian	17 (70.8)	17 (77.3)	.22
Asian	4 (16.7)	3 (13.6)	
Black/African American	3 (12.5)	0	
More than one race	0	2 (9.1)	
Hispanic ethnicity, N (%)	3 (12.5)	0	.23
Years of education, mean (SD) [range]	16.7 (1.63) [13–20]	16.4 (2.28) [12–22]	.66
Marital Status, N (%)			
Married or partnered as if married	15 (62.5)	14 (63.6)	1
Never Married	4 (16.7)	3 (13.6)	
Divorced/Annulled	4 (16.7)	3 (13.6)	
Widowed	0	1 (4.5)	
Other	1 (4.2)	1 (4.5)	
Relative with dementia, N (%)			
Parent	12 (50)	6 (27.3)	.24
Spouse / partner	10 (41.7)	12 (54.5)	
Other	2 (8.3)	4 (18.2)	
Living with care recipient, N (%)	20 (83.3)	14 (63.6)	.18
Years caregiving, mean (SD) [range]	6.2 (4.2) [0.6–17]	4.2 (2.5) [.9–10]	.06
Time spent caregiving, mean (SD) [range], h per week	59.9 (48.5) [5.5–168]	63.3 (44.8) [4.0–154]	.81
Practice Meditation, N (%)	13 (54.2)	13 (59.1)	.77
Tried psychotherapy or support group, N (%)	19 (79.2)	19 (86.4)	.70
Current MDD diagnosis, N (%)	9 (37.5)	7 (31.8)	0.78
MDD episodes (lifetime), mean (SD) [range]	0.9 (1.5) [0–6]	3.0 (8.4) [0–40] *	.33
Current antidepressants, N (%)	5 (20.8)	6 (27.3)	.73
Lifetime antidepressant trials, mean (SD) [range]	0.9 (1.4) [0–4]	0.9 (1.5) [0–5]	.94

Abbreviations: h, hours; MDD, Major Depressive Disorder; SD, Standard Deviation; y, years.

* If outlier of 40 MDD Episodes is excluded, the mean, SD and range are 1.2 (1.6) [0–5]

Table 2.

Psychological outcomes between groups: affective symptoms and positive traits

		Ratings per group, No.		Mean (SD)		Mean change [95% CI]			
Measure	**Timepoint**	**MIT**	**SG**	**MIT**	**SG**	**MIT**	**SG**	***d***	***P***
Self-Rated Depression	Screening	24	22	12.2 (7.0)	11.7 (4.8)				
	Week 1	19	16	10.8 (6.0)	12.0 (4.3)	−1.9 [−4.5, 0.7]	0.0 [−1.4, 1.5]	−.4	.1
	Week 2	19	20	8.9 (5.2)	10.2 (5.8)	−4.2 [−6.0, −2.3]	−1.4 [−3.0, 0.2]	−.7	.2
	Week 3	21	18	6.8 (3.9)	8.0 (4.5)	−4.5 [−7.1, −1.9]	−3.2 [−5.4, −1.1]	−.2	.2
	Week 4	21	18	6.8 (3.5)	8.3 (4.0)	−4.8 [−7.3, −2.4]	−2.3 [−3.8, −0.8]	−.5	.1
	Post group	24	21	7.2 (3.5)	9.9 (4.7)	−5.0 [−7.3, −2.7]	−1.8 [−3.9, 0.2]	−.6	.03
	4 months	20	19	7.2 (5.1)	10.2 (4.7)	−4.6 [−7.2, −1.9]	−1.3 [−3.3, 0.7]	−.6	.003
Clinician-Rated Depression	Screening	24	22	9.9 (6.8)	10.0 (6.1)				
	Post group	24	21	4.3 (4.1)	9.9 (6.2)	−5.5 [−7.9, −3.2]	−0.4 [−2.7, 1.9]	−.9	.0002
	4 months	16	17	3.8 (5.7)	9.3 (5)	−6.5 [−8.7, −4.3]	−0.2 [−2.4, 2.0]	−1.0	.0001
Anxiety	Screening	24	22	44.7 (13.9)	46.8 (10.4)				
	Post group	24	21	36.3 (9.9)	42.7 (10.6)	−8.4 [−11.1,−5.8]	−4.4, [−7.1,−1.8]	−.4	.005
	4 months	19	19	34.5 (11)	42.9 (10.4)	−8.7 [−11.5, −5.8]	−3.5 [−6.3, −0.6]	−.5	.002
Negative Affect	Screening	24	22	21.8 (9.8)	24.0 (7.3)				
	Post group	24	21	17.4 (7.4)	18.9 (5.5)	−4.4 [−7.5, −1.3]	−4.8 [−7.9, −1.6]	.04	.2
	4 months	18	18	17.3 (7.4)	19.3 (5.3)	−3.9 [−7.3, −0.5]	−3.7 [−7.1, −0.2]	.03	.1
Caregiver Burden	Screening	23	22	46.6 (14.1)	43.7 (15.3)				
	Post group	24	21	40.7 (13.2)	43 (14.1)	−5.7 [−10.1, −1.4]	−1.9 [−6.2, 2.5]	−.4	.3
	4 months	18	18	35.7 (11.2)	36.6 (11.5)	−6.6 [−11.1, −2.2]	−6.4 [−10.9, −2.0]	−.02	.7
Well-being	Screening	24	22	41.8 (10.5)	41.8 (11.3)				
	Post group	24	21	50.2 (7.2)	43.9 (13.0)	8.5 [5.2, 11.8]	2.3 [−1.0, 5.6]	.7	.005
	4 months	20	19	52.0 (10.2)	43.5 (11.9)	8.9 [6.3, 11.4]	0.1 [−2.5, 2.7]	.9	.0005
Self Compassion	Screening	24	22	38.2 (8.2)	34.6 (7.7)				
	Post group	24	21	41.8 (7.6)	36.7 (7.2)	3.7 [1.0, 6.3]	2.0 [−0.7, 4.6]	.3	.007
	4 months	18	18	43.0 (8.5)	38.1 (7.2)	4.1 [1.9, 6.3]	3.5 [1.3, 5.7]	.1	.02
Positive Affect	Screening	24	22	29.7 (7.8)	30.1 (7.3)				
	Post group	24	21	34.5 (6.6)	31.4 (8.2)	4.9 [2.7, 7.1]	1.7 [−0.6, 3.9]	.4	.06

		Ratings per group, No.		Mean (SD)		Mean change [95% CI]			
Measure	**Timepoint**	**MIT**	**SG**	**MIT**	**SG**	**MIT**	**SG**	***d***	***P***
Trait Mindfulness	4 months	18	18	36.9 (6.0)	31.3 (7.8)	6.4 [3.6, 9.2]	0.8 [−2.0, 3.6]	.7	.007
	Screening	24	22	134.8 (20.9)	129.9 (19.1)				
	Post group	24	21	146.5 (16.5)	135 (17.6)	11.7 [5.8, 17.6]	5.0 [−0.9, 10.8]	.5	.006
	4 months	19	18	151.4 (18.5)	130.9 (18.4)	13.1 [6.3, 19.9]	2.8 [−3.9, 9.6]	.6	.0004
Acceptance and Action	Screening	23	22	18.5 (8.7)	23.5 (9.4)				
	Post group	24	21	15.3 (8.2)	21.2 (8.9)	−3.1 [−5.3, −0.9]	−2.0 [−4.2, 0.3]	−.2	.003
	4 months	18	18	14.1 (8.2)	19.1 (8.0)	−3.1 [−5.5, −0.6]	−3.2 [, −5.6, −0.7]	.02	.007

MIT = Mentalizing Imagery Therapy; SG = support group; each prior timepoint was included in the mixed linear model for the subsequent timepoint.

p values represent Time × Group effects for final models including Time, Age and Sex as covariates.