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Featured Article

The Age-Well observational study on expert meditators in the Medit-Ageing European project

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Abstract

Introduction: The Age-Well observational, cross-sectional study investigates the affective and cognitive mechanisms of meditation expertise with behavioral, neuroimaging, sleep, and biological measures sensitive to aging and Alzheimer's disease (AD).

Methods: Thirty cognitively unimpaired individuals aged 65 years or older with at least 10,000 hours of practice in mindfulness meditation (MM) and loving-kindness and compassion meditation (LKCM) are selected. The outcomes are the neuroimaging brain correlates of MM and LKCM and the assessments of long-term meditation practices on behavioral, neural, and biological measures as compared to nonmeditator older controls from the Age-Well randomized controlled trial.

Results: Recruitment and data collection began in late 2016 and will be completed by late 2019.

Discussion: Results are expected to foster the understanding of the effects of meditation expertise on aging and of the mechanisms of action underlying the meditation intervention in the Age-Well randomized controlled trial. These finding will contribute to the design of meditation-based prevention randomized controlled trials for the aged population and to the exploration of the possible long-time developmental trajectory of meditation training.

Keywords: Aging; Alzheimer's disease; Dementia; Prevention; Cognition; Reserve; Meditation expertise; Mindfulness meditation; Compassion and loving-kindness meditation; Emotion; Lifestyle; Neuroimaging; Blood markers; Sleep

The authors declare no conflicts of interest.

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1. Introduction

There is a recent interest for using meditation practice to improve mental health and well-being in the aging population and reduce risks for Alzheimer's disease (AD) [1–5], yet there is still a paucity of evidence supporting this hypothesis. We are currently exploring this hypothesis in the Medit-Ageing research project, which is funded by the European Commission under the call PHC22-2015 of the Horizon 2020 research and innovation program (grant agreement No 667696; public name: Silver Santé Study; www.silversantestudy.eu). This project includes 10 partners from six European countries (Belgium, France, Germany, Spain, Switzerland, and United Kingdom). It aims at assessing the impact of meditation practice on mental health and well-being in aging populations. Medit-Ageing includes two independent randomized controlled trials (RCTs) sponsored by Inserm, that is, the Subjective Cognitive Decline-Well (SCD-Well) RCT (Marchant et al., 2018) and the Age-Well RCT (Poisnel et al., 2018), as well as one cross-sectional study, that is, the Age-Well observational study. The aim of this article is to present the design, hypotheses, and progress of the Age-Well observational cross-sectional study. This later complements the Age-Well RCT by investigating a group of older expert long-term meditators.

More specifically, the Age-Well observational study's first aim is to identify the brain signatures of specific meditation practices. Indeed, the Age-Well RCT includes an 18-month original secular program of meditation training to both mindfulness meditation (MM) and loving-kindness and compassion meditation (LKCM). However, the Age-Well RCT cannot parcel out the specific contribution of each meditation practice: its 18-month postintervention visit characterizes only the combined effect of MM and LKCM on mental health and well-being in the aging population. The Age-Well observational cross-sectional study will allow to highlight brain changes specifically associated with each of these meditation states (i.e., MM vs LKCM; Fig. 1A) using functional magnetic resonance imaging (fMRI) data

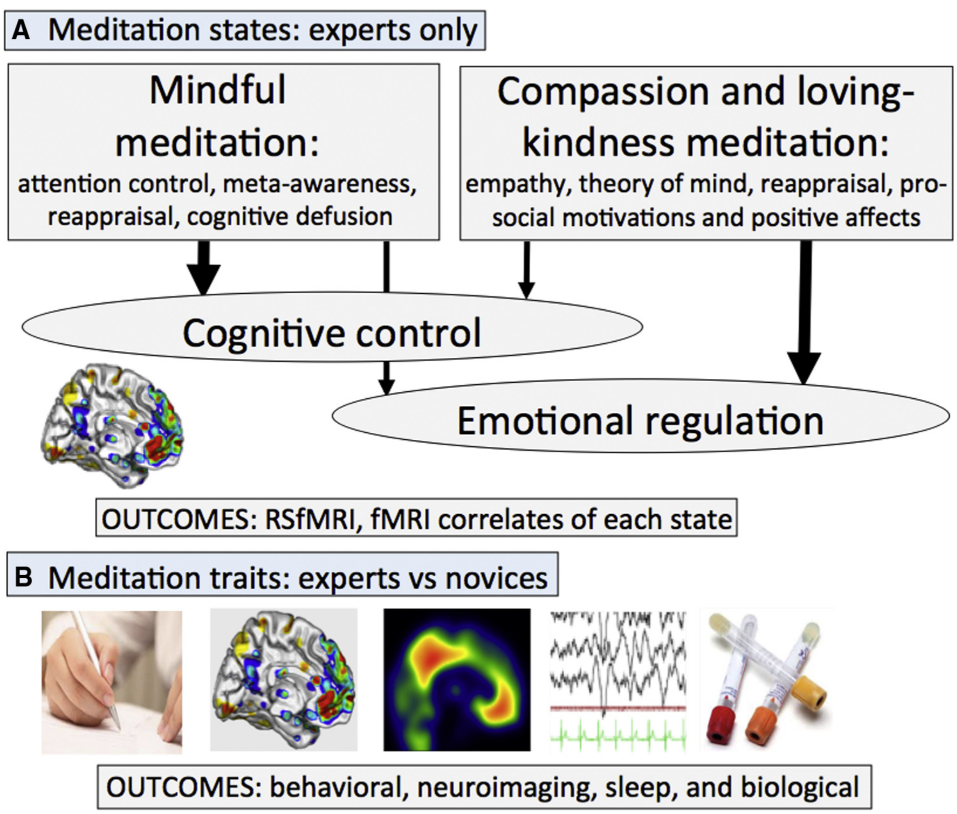

Fig. 1. (A) Meditation states: Hypothetical model of the core mental processes cultivated during mindfulness and compassion and loving-kindness meditations. Both states are thought to enhance cognitive control and positive emotions, mindfulness meditation enhancing particularly the former, and compassion meditation the latter (see arrows). Through these mechanisms, both practices are expected to have a positive impact on emotional balance, well-being, and emotion regulation and more broadly, on mental health and well-being in aging. The Age-Well observational study aims to characterize the neural correlates of these two states in expert meditators using resting-state fMRI (RS-fMRI) functional connectivity measures, and a neuroimaging affective paradigm. The neural markers will be used to assess the specific contribution of each practice in the meditation intervention implemented in the Age-Well clinical study (Poisnel et al. 2018). (B) Meditation trait: Meditation expertise (i.e., trait) will be assessed by comparing expert and novice meditators on a variety of measures sensitive to aging and well-being. The outcomes include structural and functional brain integrity using structural and functional MRI measures sensitive to aging and behavioral measures (cognition, lifestyle, well-being, mindfulness, psychoaffective factors, and prosocialness), blood-based biological measures, sleep measures (actigraphy, polysomnography, and somnoart), and neuroimaging measures (FDG and florbetapir-PET, resting-state EEG, auditory ERP).

collected during the self-generation of these meditation states at rest (resting-state fMRI [RS-fMRI]) as well as during and after witnessing others' suffering in emotional video clips, and to assess their relative regulatory effects on cognitive control and emotions.

The second aim of the Age-Well observational study is to obtain novel markers of meditation expertise (i.e., meditation trait, Fig. 1B) in healthy older meditation expert participants. Indeed, largely due to the novelty of this research, most of our knowledge on the expected effects of meditation practice on mental health and well-being in aging is currently based on the existing literature on younger meditators. Further knowledge is needed in older expert meditators to refine the hypotheses and effect size calculation of future meditation-based intervention studies in older adults. The Age-Well observational study will collect, in the same group of older expert meditators, detailed cognitive, behavioral, biological, neuroimaging, and sleep measures of mental health and well-being. The findings could then be used to refine the predictions and interpretations of the results obtained in the meditation novices of the Age-Well RCT (where the same measures are collected) and also to determine the most sensitive measures to meditation practice in older populations for future studies. More broadly, these markers will inform the collective effort to improve instruments and assessment methods to characterize prevention studies in the field of aging and AD [6].

More specifically regarding the first aim of investigating MM and LKCM (Fig. 1A), MM can be conceptualized as a state of vigilant awareness of one's own thoughts, actions, emotions, and motivations [7,8]. The practitioner learns to intentionally pay attention to his or her internal or external experiences in the present moment, without making any value judgment. The happy mental states (mental calm) or unhappy mental states (ruminations and destructive emotions) are observed without identifying with or being absorbed by these experiences. The present moment is lived in a more open and flexible way and is less dominated by mental conditioning, which itself is considered as a source of suffering [8–10]. Accumulating clinical, behavioral, and neuroimaging evidence indicates that the sustained practice of MM improves cognition in young adults, mainly in the domains of attention, meta-cognition, and memory [8], which are cognitive processes particularly sensitive to aging and AD [3,4,8]. Eight-week mindfulness-based psychotherapies are effective especially for stress management and the prevention of relapse into depression [11–13] and could also influence cardiovascular risk factors [14]. Training in MM, ranging from 8 weeks to 3 months, specifically impacts brain networks associated with attention, memory, and meta-cognition, in particular, the frontoparietal attention networks, the salience network (insula and anterior cingulate cortex [ACC]), and more broadly the frontopolar cortex [15,16]. Complementing MM, the practice of LKCM aims to orient one's attention toward others by cultivating feelings of benevolence and kindness and to increase the motivation to help alleviating others' suffering (i.e., compassion) and to help increasing others' well-being (i.e., loving-kindness) [17,18]. Before developing these prosocial attitudes, compassion-meditation-based interventions often start by nurturing a relationship of greater benevolence toward oneself, for instance by addressing emotions such as shame, self-criticism, or anger with more acceptation and kindness [17,18]. Even if the role of cognitive processes in LKCM is still debated [19,20], these processes should include empathy, theory of mind, reappraisal, prosocial motivation, and the self-generation of positive affect [18,21–23]. Recent evidence suggests that LKCM could also downregulate stress, depression, and cardiovascular risk factors [24,25]. Moreover, neuroimaging evidence shows that empathy, mentalizing, and attention reorienting differentially predict altruistic decision-making [26] and that the state of LKCM modulates one's response to human suffering by enhancing the responses of empathy-related brain regions, such as the insula, as well as by augmenting activity in brain regions associated with positive affect and affiliation, such as the striatum and the medial orbitofrontal cortex [27–29]. A recent longitudinal study comparing within the same participants the effect of a 3-month attention-based meditation training with a 3-month compassion-related meditation training found differential training-related anatomical changes in attention and emotion regulation-related brain areas, the former inducing cortical thickness changes in prefrontal regions, whereas the latter inducing cortical thickness changes in frontoinsular regions [16]. Based on this emerging literature in young adults, we hypothesize that these two styles of meditation will be engaging common but also distinct cognitive and emotional processes as summarized in Fig. 1A, which should be correlated to partly overlapping and partly specific neural correlates in frontoparietal and limbic networks. We hypothesize that RS-fMRI data collected during the self-generation of these meditation states will be correlated with changes in spontaneous functional connectivity in these attention and affective brain areas. We also hypothesize that the two practices will affect the processing of others' suffering as well as the recovery from emotional challenges as measured by fMRI during and after witnessing others' suffering in emotional video clips. More specifically, we predict that meditators reporting either enhanced empathy and/or positive affective experiences and/or mentalizing strategy during LKCM will exhibit enhanced brain activations in the core neural networks commonly activated during empathy (e.g., anterior insula), positive affects or affiliation (e.g., medial orbitofrontal cortex and striatum), or theory of mind (e.g., temporoparietal junction). We also predict that the duration of neural activation patterns associated with threat perception (amygdala, thalamus, insula, dorsal ACC) in the rest period following the videos will be reduced particularly during MM and LKCM compared to the control condition without meditation instructions [30]. These brain changes, specifically associated with MM or LKCM meditations, will be used as neural signatures of these meditation states. They will allow notably to weight the relative contribution of each meditation practice in the changes observed in the novices of the Age-Well RCT.

The second aim of the Age-Well observational study is to characterize the effects of meditation expertise on the same behavioral, neuroimaging, sleep, and biological measures as the ones collected in the Age-Well RCT (Fig. 1B). Overall, we hypothesize that meditation expertise will be associated with increases in positive emotions and cognitive control measures compared to nonmeditator older controls. These increases in turn are expected to be associated with positive effects on markers of health, cognitive function, and well-being in aging. One measure of particular importance will be the primary outcomes of the Age-Well RCT, which measure structural and functional neuroimaging markers of brain integrity. Based on our pilot study [31], we predict that meditation expertise will be associated with greater volume and perfusion in the ACC and insula compared to nonmeditator older controls.

2. Methods/design

2.1. Clinical trial setting and design

The Age-Well observational, cross-sectional study is a monocentric trial with 30 autonomous and motivated cognitively normal older expert meditators aged $\geq$65 years. The clinical trial protocol (EudraCT: 2016-002441-36; IDRCB: 2016-A01767-44, ClinicalTrials.gov Identifier: NCT02977819) adheres to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines for clinical trial protocols [32].

2.2. Participant recruitment and prescreening

Expert meditators should have extensive practices in two families of Buddhist meditations: MM (i.e., Samatha/Vipassana, or Zazen [Zen], Shikantaza [Zen], one-pointed focused attention, or Mahamudra/Dzogchen in Tibetan Buddhism), and LKCM (e.g., Tonglen meditation, practices on the Four Immeasurables [e.g. metta meditation], meditation on Bodhicitta). Expert meditators are recruited in Europe through flyers, advertisement in Buddhist magazine, e-mails, and presentations in Buddhist meditation retreat centers. Interested practitioners are invited to fill in a questionnaire to prescreen the individuals who fit with the main eligibility criteria.

2.3. Participant selection: Eligibility criteria and screening visit (V0)

Motivated participants corresponding to the target population are invited to the screening visit (V0) where complete written and oral information is provided and an informed consent is signed. The screening visit comprises a medical interview and a cognitive assessment with a neuropsychologist where the diagnostic battery tests are performed (see Poisnel et al. 2018 for details). Inclusion and exclusion criteria for participants in the Age-Well observational study are detailed in Table 1. Briefly, participants are cognitively normal older individuals (aged $\geq$ 65 years), with no major neurological or psychiatric disorder, with an intensive and regular practice of meditation (i.e., at least 10,000 hours of formal meditation in their life including at least 6 cumulative months spent in retreat [at least 8 hours per day of formal meditation] and a regular daily meditation practice, at least 6 days a week of at least 45 minutes of meditation, proficiency in MM and LKCM). The medical doctor verifies these criteria and performs a general health screening comprising medical history, drug therapies, measurement of height and weight, hip and waist circumferences, and sitting blood pressure.

2.4. Measures collected at V1

Fig. 1A describes the measures collected only for experts, and Fig. 1B describes the measures collected for experts and for novices who participate in the Age-Well RCT (Poisnel et al. 2018). The former ones are used to assess meditative states, the latter ones to assess meditation-related traits, such as meditation expertise. The detailed biological, behavioral, neuroimaging, and sleep measures collected at the V1 visit are listed in Poisnel et al. 2018. Briefly, behavioral measures include a series of neuropsychological tests, scales, and questionnaires particularly sensitive to aging and AD (e.g., assessing episodic memory, attention, and executive functions) and/or meditation practices (e.g., assessing well-being, mindfulness and meta-cognition, emotion regulation, altruism, and prosociality), or to assess different aspects of sleep quality, lifestyle, and quality of life. Neuroimaging measures include a series of structural and functional (resting-state and task-related) MRI scans, FDG- and florbetapir-PET scans, and resting-state EEG and auditory event-related potential recording. Objective measures of sleep include actigraphy, somnoart, and polysomnography, and biological measures are obtained from blood sampling. All assessment procedures were discussed and audited by experienced and skilled study staff to ensure the standardization of the procedures.

2.5. Blinding

As the expert meditators' data were collected between the three successive cohorts spaced about 6 months apart of the Age-Well Clinical RCT, the interviewers, psychometrists, and outcome assessors were not blind to the group condition.

2.6. Outcome measures

The outcomes of the Age-Well observational study are listed in Table 2. As depicted in Fig. 1A, the first objective is to measure the differential engagement of brain areas

Table 1
Inclusion and exclusion criteria for the Age-Well observational study

Inclusion criteria	Exclusion criteria
Age ≥ 65 years	Safety concerns in relation to MR scanning (claustrophobia, ferromagnetic object) or PET scanning (Blood sampling to check hepatic and renal functions are performed before the PET scans; known hypersensibility to Amyvid or Glucotep)
Autonomous	Presence of a major neurological or psychiatric disorder (including an addiction to alcohol or drugs)
Living at home	History of cerebral disease (vascular, degenerative, physical malformation, tumor, or head trauma with loss of consciousness for more than an hour)
Educational level ≥ 7 years (from the preparatory course—first grade—included)	Presence of a chronic disease or acute unstable illness (respiratory, cardiovascular, digestive, renal, metabolic, hematologic, endocrine, or infectious)
Registered to the social security system	Current or recent medication that may interfere with cognitive functioning (psychotropic, antihistaminic with anticholinergic action, anti-Parkinson's, benzodiazepines, steroidal antiinflammatory long-term treatment, antiepileptic, or analgesic drugs), the interfering nature of the different treatments being at the discretion of the investigating doctor
Motivated to effectively participate in the project and signing the informed consent form	Being under legal guardianship or incapacitation
Performance within the normal range on standardized cognitive tests according to agreed study-specific standards (age, sex, and education level when available)	Participation to another biomedical research protocol including the injection of radiopharmaceuticals
10,000 hours of formal meditation in their life including at least 6 cumulative months spent in retreat	Physical or behavioral inabilities to perform the follow-up visits as planned in the study protocol
A regular daily meditation practice, at least 6 days a week of at least 45 minutes of meditation	
Extensive experience in mindfulness meditation [i.e., mindfulness, Samatha/Vipassana, Zazen (Zen), Shikantaza (Zen), focused attention, Mahamudra/Dzogchen] and loving-kindness and compassion meditation (i.e., Tonglen practice, 4 incommensurables qualities practice [metta/karuna], Bodhicitta meditation)	

implicated in cognitive control and emotion regulation during two forms of meditation (MM and LKCM) as measured by RS-fMRI and task-related fMRI. The second objective is to test whether behavioral, neuroimaging, biological markers of aging, well-being, and cognition are positively affected by meditation expertise (Fig. 1B). The endpoints will be the mean differences in the measures cited above between the older expert meditators and the nonmeditator older controls from the Age-Well RCT. Of particular interest will be to test whether meditation expertise is associated with superior volume and perfusion activity of the anterior cingulate cortex and the insula compared to nonmeditator older controls from the Age-Well RCT, which will corroborate the hypothesis of the primary outcome of the Age-Well RCT [33,34].

2.7. Statistical considerations

2.7.1. Sample size calculation

Studies in experienced meditators assessing compassion meditation-related changes in fMRI brain activity showed an effect size (calculated for the fMRI change in the insula in response to emotional stimuli) of d = 0.74 [35]. Our power to detect a significant group difference at a $P = .05$ α level, 2-tailed with an n of 30 per group will thus be in the range of 0.80.

2.7.2. Volunteer characteristics

Appropriate descriptive statistics for demographic, disease history, and baseline characteristics will be presented to compare the expert meditators with nonmeditator older controls from the Age-Well RCT. Categorical variables will be presented as the number and percentage of volunteers in each category. Continuous variables will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, and maximum).

2.7.3. Analysis of the endpoints

Paired sample *t*-tests or Wilcoxon tests (for non-normally distributed parameters) will be performed to compare the behavioral and neuroimaging measures collected during MM and LKCM. Two sample t-tests or Mann-Whitney tests (for non-normally distributed parameters) will be used to compare the other biological, neuroimaging, and behavioral measures in the expert meditators versus the nonmeditator older controls from the Age-Well RCT.

If the distribution of baseline confounding factors (age, education, gender, Mini–Mental State Examination) is unbalanced between groups, the main and sensitivity comparative analyses will be performed with adjustment on those factors. An exploratory analysis of the effect of the exposure to meditation (number of hours of practice in life) will be performed with available data using appropriate models.

Table 2
List of collected measures and corresponding outcomes

Measures collected at V1	Outcomes
Behavioral measures (Poisnel et al. 2018 for details): Series of neuropsychological tests, scales, and questionnaires particularly sensitive to aging and AD (e.g., assessing episodic memory, attention, and executive functions) and/or meditation practices (e.g., assessing well-being, mindfulness and meta-cognition, emotion regulation, altruism, and prosociality), or as they allow to assess different aspects of sleep quality, lifestyle, and quality of life.	Composite scores and raw individual measures of cognitive performance, well-being, mindfulness and meta-cognition, emotions, emotion regulation, altruism, prosociality, sleep quality, lifestyle, and quality of life of the participants. Partner perception of the participant's well-being, willingness to help, social interactions, and memory capacity.
Neuroimaging measures (Poisnel et al. 2018 for details):	
1. Structural MRI	
(a) 3D T1 and fluid-attenuated inversion recovery (FLAIR)	- Gray and white matter volume - White matter lesions (number and size per type and location)
(b) High-resolution proton-density focused on the hippocampus	- Hippocampal subfield volumes
(c) Diffusion Kurtosis Imaging (DKI)	- Fractional anisotropy and mean diffusivity
(d) Quantitative Susceptibility Mapping (QSM)	- Magnetic susceptibility index
2. Functional MRI -fMRI	
(a) Resting-states fMRI (at rest, mindfulness meditation [MM], and loving-kindness and compassion meditation [LKCM])	- Brain functional connectivity
(b) Task-related fMRI	
i) The AX-CPT task [1]	- Behavioral and brain activity measures associated with attentional processes (alertness, inhibition, sustained attention)
ii) The SoVT-Rest task (without meditation-specific instructions, MM, and LKCM)	- Behavioral and brain activity and connectivity changes associated with emotions and emotional inertia
3) Resting-state EEG	- Resting-state spontaneous oscillatory activity
4) Auditory event-related potential (ERP) using the mismatch negativity protocol [2]	- ERP measures of brain activity associated with auditory mismatch negativity
5) PET scans	
(a) Glucotep (FDG)-PET scan	- Resting-state brain glucose consumption
(b) Amyvid (Florbetapir, AV45)-PET scan	- Brain perfusion from early florbetapir-PET acquisition - Brain amyloid load from late florbetapir-PET acquisition
Biological measures from blood (Poisnel et al. 2018 for details): Fasting sampling performed in the morning and after one day of diet excluding serotonin-rich food (tomatoes, avocados, pineapple, chocolate, bananas, etc.). 18 tubes (68 mL) of blood collected at V1 and 16 tubes (62 mL) at V3.	- Global health: blood count, glucose, cholesterol/lipid profile, urea, creatinine, γ-glutamyltransferase, glutamic oxaloacetic transaminase, Glutamic pyruvic transaminase, brain natriuretic peptide, thyroid-stimulating hormone - Stress/inflammation: high-sensible C-reactive protein, cytokines, cortisol, superoxide dismutase - Aging/AD (telomere length, telomerase activity, β-amyloid (Aβ) 1-40/42, total tau, phospho-tau, tissue plasminogen activator, plasminogen activator inhibitor-1, brain-derived neurotrophic factor, insulin, insulin growth factor-1, lymphocyte immunophenotyping, repressor element 1-silencing transcription factor, neurofilament - Mood: serotonin, - Sex/gender: bioavailable testosterone, estradiol, sex hormone binding globulin, dehydroepiandrosterone sulfate - Genetic: Apolipoprotein E, Genome Wild Association Study - Epigenetics
Objective measures of sleep:	
1) 1-week wrist actigraphy recording	- Indices of mean sleep duration, sleep fragmentation and regularity of the rest-activity cycle obtained from activity and resting state
2) 2-nights at-home polysomnography	- Multiple indices of sleep quality
3) A 2D-object location task performed before and after night sleep	- Behavioral measures of overnight memory consolidation

Analyses with neuroimaging data will include both voxel-wise and region-of-interest-based analyses. For fMRI data analysis, we will be using several statistical packages: SPM software (Wellcome Trust Centre for Neuroimaging, London), PLS [36,37], and CONN toolbox (www.nitrc.org/projects/conn, RRID:SCR_009550, [38]) on Matlab (MathWorks, Natick, MA). For other statistical analyses, we will use R statistical software [39], SAS (https://sas.com), IBM SPSS Statistics for Windows (Armonk, NY; IBM Corp) and Statistica (StatSoft, Dell Software).

2.8. Ethics and safety aspects

The Age-Well observational study was approved by the local ethics committee (Comité de Protection des Personnes CPP Nord-Ouest III, Caen; trial registration number:

EudraCT: 2016-002441-36; IDRCB: 2016-A01767-44). The study conforms to the principles of good clinical practice. Participants give their written informed consent before enrollment in the study. The sponsor of the clinical trial has insurance for all participants. The disadvantages and risk of adverse events in the present study are considered as low. Blood samples are drawn from the antecubital vein after disinfection with alcohol swabs. There is a minimal risk of infection and bleeding related to the procedure. There are no known side effects to MRI, but the procedure can be uncomfortable. A thorough anamnesis is carried out during the medical examination to account for contraindications (metal implants, etc.). Unexpected findings will be dealt with according to local hospital guidelines.

2.9. Data management and monitoring

The sponsor (Inserm) has established a trial steering committee according to Good Clinic Practice guidelines with the responsibility to provide oversight of the conduct of the trial, advice on scientific credibility on behalf of the sponsor and the funder, and to assess the progress of the protocol. An external Data and Safety Monitoring Board (DSMB) independent of the sponsor was appointed to (1) evaluate the safety of participants included in the Age-Well trial and (2) recommend preserving the scientific and the ethical integrity of the study.

More details on data management and monitoring can be found in Poisnel et al. (2018).

2.10. Study progress

From May 2016 to September 2018, 45 individuals responded to flyers, conferences at meditation centers, in-person request, and e-mail request. Among those, 21 participants were interested in participating and screened (V0 visit) and 20 were included (70% men and 30% women). The reason for noninclusion was abnormal performance in the diagnostic battery. Recruitment will be achieved in late 2019. Electronic data entry and processing is currently ongoing.

3. Discussion

The Age-Well observational study is part of the Medit-Ageing project, a European research initiative to foster healthy aging and older adults' well-being by understanding factors that could prevent and delay age-related diseases and disabilities. It is the first cross-sectional study to exhaustively explore the relationship between meditation expertise, aging, and well-being with a multidisciplinary, multimodal approach that combines behavioral, neuroimaging, sleep, and biological measures. The close association of the Age-Well observational study with the Age-Well RCT will enable the identification of novel markers of meditation expertise in healthy older meditators and the refinement of hypotheses and interpretations in the Age-Well RCT. Studying the neural correlates of MM and LKCM will enable us to better characterize the specific contribution of two styles of meditation training on cognitive control and emotion regulation. A better understanding of the mechanisms of action of meditation will facilitate sensitivity to intervention analysis and help refine and tailor future meditation-based interventions. Understanding these regulatory training regimes is crucial in aging as psychoaffective factors such as stress, anxiety, and depression, significantly contribute to reduced quality of life and increased risk for dementia in older adults [40–42].

An important limitation of the study comes from its cross-sectional design that prevents us from studying any causal relationship associated with meditation practice. In particular, it is possible that some group differences will reflect other factors such as difference in worldview, lifestyle, or diet. By collecting quantitative and qualitative measures of many of these lifestyle factors, we will be able to explore some of these alternative interpretations, even if this study will not be able to disentangle whether these factors influenced meditation practice (i.e., confounding factor) or were influenced by meditation practice (i.e., mediation factor of meditation practice). As we collected identical measures in the longitudinal Age-Well RCT, we will be able to address some of these interpretative limitations by identifying the expert-related effects in the Age-Well observational study, which are overlapping, or not, with the training-related effects from the Age-Well RCT. From this comparison, we might be able to simulate the possible long-time developmental trajectory of meditation training beyond the 18 months of training used in the Age-Well RCT. This comparison will guide future research designs concerned with optimizing the duration of a meditation training for the elderly. Another limitation comes from the heterogeneity of the meditation traditions. In particular, the various traditions weight somewhat differently on the relative role of MM and LKCM in the training. However, this heterogeneity can also be viewed as a strength. The different Buddhist traditions represented here (Zen, Theravada, and Tibetan Buddhism) will help to generalize any observed effect beyond particular traditions. Post hoc analyses will explore the influence of individual meditation practice preferences on the measures. The extended plan will be to compare the effects on aging of various domains of expertise such as meditation, sport, music, and chess.

Using an innovative approach, results from the Age-Well studies are expected to improve understanding of the mechanisms through which different forms of meditation may foster healthy aging and older adults' well-being, in addition to preventing and delaying age-related diseases and disabilities. The Age-Well observational study should help shape and optimize future lifestyle- and meditation-based clinical trials and facilitate the integration of meditation practice into existing and future preventive programs and clinical interventions for older people.

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RESEARCH IN CONTEXT

1. Systematic review: We identified observational trials by searches of clinicaltrials.gov. Search terms: Condition or disease: ageing; healthy; Age: senior (accepts healthy); Study type: observational; other terms: prevention. Two studies were identified.

2. Interpretation: The Age-Well observational study is the first observational study to assess the specific cognitive and affective brain correlates of two distinct styles of meditation and the effects and mechanisms of long-term meditation practice on behavioral, neuroimaging, sleep, and biological markers of mental health and well-being in the aging population. This study addresses whether older expert meditators have enhanced brain and cognitive reserve, emotion regulation, well-being, sleep, global health, and quality of life compared to nonmeditator older controls.

3. Future directions: The Age-Well observational study will contribute to the design of meditation-based prevention randomized controlled trials and to the exploration of the possible long-time developmental trajectory of meditation training.

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