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Decoding meditation mechanisms underlying brain preservation and psycho-affective health in older expert meditators and older meditation-naive participants

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Meditation is a mental training approach that can improve mental health and well-being in aging. Yet the underlying mechanisms remain unknown. The Medit-Ageing model stipulates that three mechanisms — attentional, constructive, and deconstructive — upregulate positive psycho-affective factors and downregulate negative ones. To test this hypothesis, we measured brain structural MRI and perfusion, negative and positive psycho-affective composite scores, and meditation mechanisms in 27 older expert meditators and 135 meditation-naive older controls. We identified brain and psycho-affective differences and performed mediation analyses to assess whether and which meditation mechanisms mediate their links.

Meditators showed significantly higher volume in fronto-parietal areas and perfusion in temporo-occipito-parietal areas. They also had higher positive and lower negative psycho-affective scores. Attentional and constructive mechanisms both mediated the links between brain differences and the positive psycho-affective score whereas the deconstructive mechanism mediated the links between brain differences and the negative psycho-affective score.

Our results corroborate the Medit-Ageing model, indicating that, in aging, meditation leads to brain changes that decrease negative psycho-affective factors and increase positive ones through relatively specific mechanisms. Shedding light on the neurobiological and psycho-affective mechanisms of meditation in aging, these findings provide insights to refine future interventions.

Biological aging can be defined as the "accumulation of molecular and cellular damage over an organismal life-span", and is associated with physical deterioration and an increased risk for developing diseases - including neurodegenerative disorders such as Alzheimer's disease (AD)[1]. Those changes are associated with cognitive decline in several domains including attention, memory, and executive functions[2]. They are also reflected in brain deterioration, including age-related decreases in gray matter volume (GMV) and glucose metabolism[3,4], and the presence of amyloid deposition[5].

There is now widespread recognition that mental health and well-being can affect biological aging and the risk for neurodegenerative diseases. Environmental factors, including modifiable lifestyle factors, can, in turn,

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influence mental health, age-related changes and dementia risk[6]. As a result, studies have emerged, highlighting how lifestyle changes can contribute to healthier brain aging and a reduced AD risk[7–9]. Among these modifiable risk factors are psycho-affective factors, with depression standing out as particularly impactful in older adults. Furthermore, research has linked depression, stress, and anxiety to adverse effects on both brain structure and function[10–12], underscoring the importance of regulating these factors for promoting healthier brain aging.

In this context, meditation, a form of mental training aimed at improving one's core psychological capacities like attention and emotional regulation[13] – holds promise for mitigating the impact of adverse psycho-affective factors thus promoting brain health and AD prevention. The Medit-Ageing model suggests that regular practice of mindfulness meditation (MM, which involves non-judgmental attention to present-moment experiences) and loving-kindness and compassion meditation (LKCM, which cultivates feelings of compassion and loving-kindness toward oneself and others) in the aging population constitutes a lifestyle that may help protect against AD. According to this model, these practices can enhance cognition, mental health, and well-being through complementary yet overlapping cognitive mechanisms, including attention control, metacognitive monitoring, emotion regulation, and pro-social capacities. Strengthening these capacities could potentially reduce the risk of AD by enhancing beneficial age-related factors, such as cognitive reserve, and reducing detrimental factors, such as stress and depression. The model hypothesizes MM as well as LKCM would be associated with brain differences that would result in both upregulation of positive psycho-affective factors and downregulation of negative ones[14]. Meditation is thought to exert these effects through three mechanisms: attentional, constructive, and deconstructive mechanisms[14,15]. The attentional mechanism involves training attentional processes such as self-regulation and monitoring to allow the non-reactive observation and flexible disengagement from the objects of experience. The constructive mechanism entails modifying the content of thoughts and emotions to strengthen positive schemas or convert negative experiences into positive ones by cultivating positive emotions and/or nurturing positive feelings through reappraisal. The deconstructive mechanism is about phenomenally interpreting thoughts, feelings, and perceptions just as mental processes rather than as accurate depictions of reality to deconstruct maladaptive self-schemas. Note that these mechanisms are skills thought to reflect qualities that are naturally present in every human being to varying degrees[16–19], specifically trained by meditation practice, and thus further developed in experienced meditators[20–23].

Our goal in this study is to test the Medit-Ageing model through assessing the role of these meditation mechanisms in mediating brain and psycho-affective differences in aging. For this purpose, we studied older expert meditators, i.e., individuals who have been intensively practicing meditation throughout their lives and who are expected to show how meditation impacts the brain and psycho-affective age-related changes. Previous studies in older expert meditators have shown lower levels of stress and anxiety as well as higher levels of quality of life compared to controls[24–27]. Although not investigated in older populations, levels of depression have also been shown to be lower in expert meditators compared to controls[28]. Brain structure and function have also been reported to be better preserved in expert meditators including older ones, with higher cortical thickness, GMV, and glucose metabolism than controls. These effects have notably been observed in regions sensitive to aging and AD such as the hippocampus, ventromedial prefrontal cortex, temporo-parietal junction, and posterior cingulate cortex (PCC)[26,29–33].

Here, our aim is to investigate the brain regions that show greater structural or functional preservation in older expert meditators compared to controls, the potential differences in both positive and negative psycho-affective factors, and the meditation-related mechanisms that may underlie those effects. Based on the Medit-Ageing model, we propose that meditation-induced brain differences will simultaneously decrease negative psycho-affective processes and increase positive psycho-affective processes through attentional, constructive, and deconstructive mechanisms. We expect these mechanisms to interact and co-act on both positive and negative psycho-affective factors. However, we hypothesize that they would partly show specificity in their action: attentional and deconstructive mechanisms, rather developed through MM practice, are expected to be more strongly linked to reduced negative psycho-affective factors, while the constructive mechanism reflecting LKCM practice is expected to be more associated with increased positive psycho-affective factors[14]. To test these hypotheses, we first conducted voxelwise analyses to identify the brain regions showing greater structural (volume) or functional (perfusion) preservation in older expert meditators compared to older meditation-naive controls. Then, we computed a composite score reflecting positive psycho-affective characteristics (from questionnaires measuring compassion, cognitive reappraisal, satisfaction with life, and well-being) and a composite score reflecting negative psycho-affective characteristics (from questionnaires measuring depression, worry, distraction, anxiety, and brooding), and tested whether meditators were characterized by higher positive and lower negative psycho-affective scores. Finally, to investigate whether specific meditation mechanisms mediated the links between meditation-induced brain differences and psycho-affective scores, we first assessed whether the meditation mechanisms related to brain differences and psycho-affective factors, and then performed mediation analyses based on the previously identified relationships, both in the entire sample and in the expert meditators only.

Results

Participants characteristics

The participants' characteristics including age, level of education, sex, global cognition, and duration of practice are presented in Table 1. Meditators were significantly more educated and included a higher proportion of males compared to controls. The two groups did not differ on the remaining variables. Meditators had, on average, 32,501 h of formal meditation practice including 16,366 h of retreat meditation.

Characteristics	Older meditation-naive controls	Older expert meditators	*p*-value
Sample size, N	135	25	-
Age, years	69.30 ± 3.8	70.29 ± 4.53	0.31
Education, years	13.15 ± 3.09	15.16 ± 3.46	**0.01**
Sex, N M/F (%)	52/83 (39/61)	16/9 (64/36)	**0.03**
MMSE	28.92 ± 1.04	29.04 ± 1.03	0.61
Formal practice (hours)	n.a	32,501 ± 31,121 (10,184–164,250)	
Retreat practice (hours)	n.a	16,366 ± 32,262 (1,461–164,250)	

Table 1. Demographics. Abbreviations: MMSE = Mini Mental State Examination, n.a not available. Values are mean ± SD (range) unless otherwise stated.

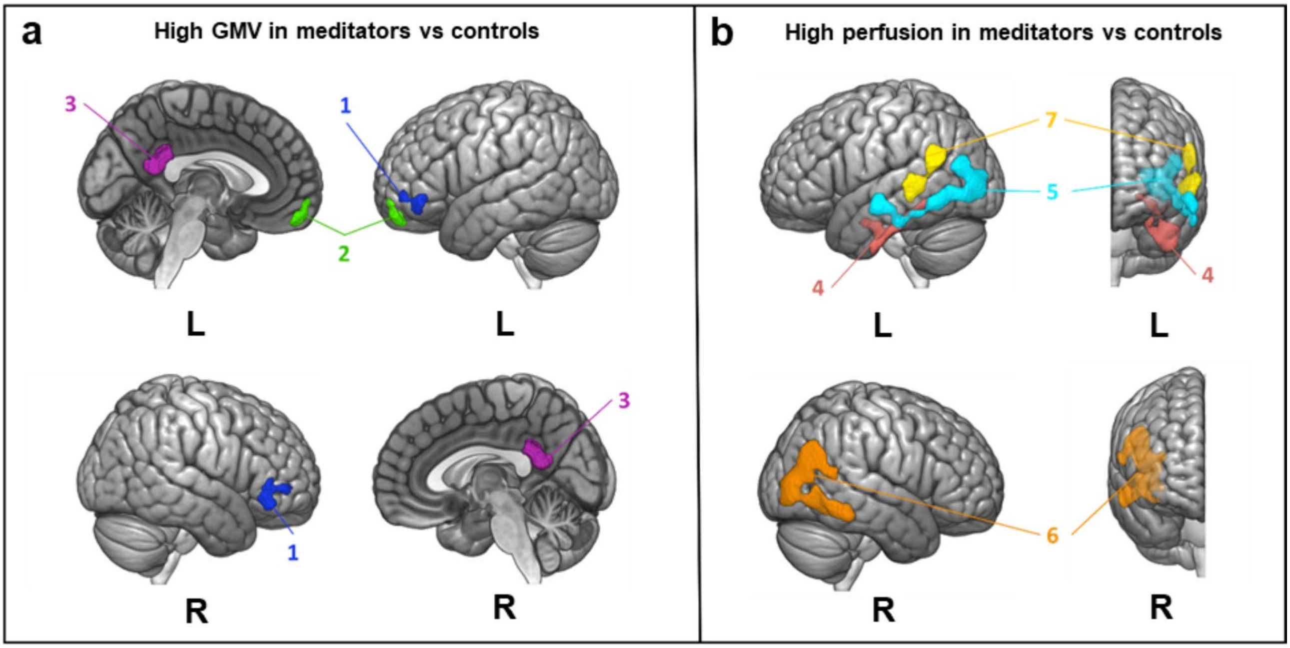


Fig. 1. Voxel-wise differences between older expert meditators and older meditation-naive controls. The results are projected on medial and external 3D brain surface views of the MNI template. The clusters indicate areas where older expert meditators showed significantly greater (**a**) GMV, gray matter volume, and (**b**) perfusion than controls. Dark blue = bilateral inferior frontal gyrus (1), Green = left orbitofrontal cortex (2), Purple = bilateral posterior cingulate cortex (3), Pink = left temporal cluster (4), Light blue = left temporo-occipital cluster (5), Orange = right temporo-occipito-parietal cluster (6), Yellow = left temporo-parietal cluster (7). Results were evaluated for significance at $p_{uncorrected}<0.005$ combined with a minimum cluster size determined by Monte-Carlo simulations using the AFNI's 3dClustSim program to achieve a corrected statistical significance of $p < 0.05$.

Brain structure and function in older expert meditators compared to meditation-naive controls

In early Florbetapir-PET analysis, meditators demonstrated significantly higher perfusion than controls in two clusters with Family Wise Error (FWE) correction ($p < 0.05$): a left temporo-occipital cluster, encompassing the left superior temporal, middle temporal, inferior temporal, and inferior and middle occipital gyri (FWE-corrected $p = 0.03$); and a right temporo-occipito-parietal cluster, including the right inferior and middle temporal, inferior and middle occipital, fusiform, and angular gyri (FWE-corrected $p = 0.01$) (Fig. 1b). When using a less stringent threshold (uncorrected $p < 0.005$), differences were also found for GMV with meditators showing more GMV than controls in the left inferior frontal gyrus (IFG; uncorrected $p = 0.047$), the right IFG (uncorrected $p = 0.02$), the left Orbitofrontal Cortex (OFC; uncorrected $p = 0.03$) and the bilateral PCC (uncorrected $p = 0.003$) (Fig. 1a). Moreover, greater perfusion in meditators than controls was found in two additional clusters at p (uncorrected) < 0.005: one including the left hippocampus, amygdala, inferior temporal gyrus and fusiform gyrus (left temporal cluster: uncorrected $p = 0.03$); and one including the left middle and superior temporal, and angular gyri (left temporo-parietal cluster: uncorrected $p = 0.03$) (Fig. 1b). Clusters' statistics are described in further details in the Supplementary Tables S1 and S2.

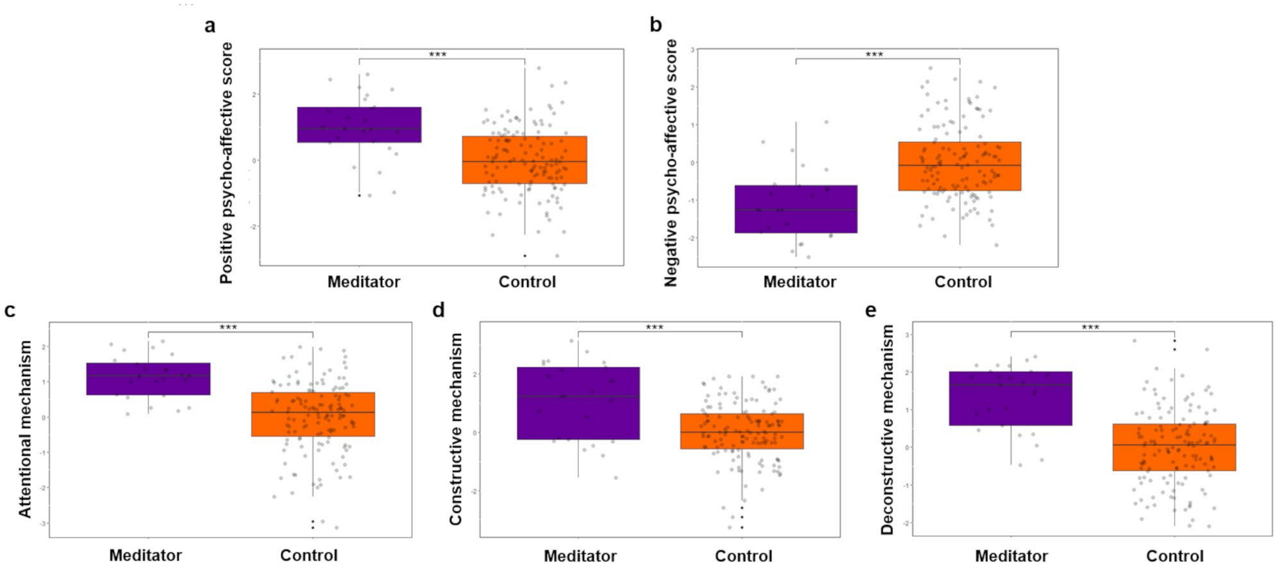


Fig. 2. Group differences for psycho-affective scores and meditation mechanisms. Boxplots illustrating the differences between the meditators (purple) and controls (orange) for the positive psycho-affective score (**a**) negative psycho-affective score (**b**), Attentional mechanism (**c**) Constructive mechanism (**d**) and Deconstructive mechanism (**e**). ***: All differences were significant with $p < 0.0001$.

Meditation mechanisms	b	SE	β	Adjusted r^2	t-value	*p*-value
Positive psycho-affective score ~ Attentional mechanism	0,39	0,08	0,38	0.13	5,06	< 0.0001
Negative psycho-affective score ~ Attentional mechanism	-0,22	0,08	-0,21	0.08	-2,71	0.007
Positive psycho-affective score ~ Constructive mechanism	0,40	0,07	0,43	0.16	5,68	< 0.0001
Negative psycho-affective score ~ Constructive mechanism	-0,12	0,08	-0,13	0.05	-1,65	0.10
Positive psycho-affective score ~ Deconstructive mechanism	0,58	0,06	0,60	0.31	8,96	< 0.0001
Negative psycho-affective score ~ Deconstructive mechanism	-0,69	0,06	-0,70	0.52	-12,39	< 0.0001

Table 2. Multiple linear regressions between each meditation mechanism and both psycho-affective scores. Abbreviations: SE Standard Error.

Differences in positive and negative psycho-affective scores between meditators and controls

Results of between-group differences on psycho-affective scores are illustrated in Fig. 2 and statistics are reported in Supplementary Table S3. Meditators reported both significantly higher positive ($F = 19.93$, $p < 0.0001$) and lower negative psycho-affective scores ($F = 17.87$, $p < 0.0001$) compared to controls.

Differences in the meditation mechanism scores in meditators versus controls

The meditation mechanisms were computed as composite scores based on questionnaires reflecting capacities manifested by each mechanism (see Materials & Methods). Results of between-group differences on meditation mechanisms are illustrated in Fig. 2 and statistics are reported in Supplementary Table S3. Meditators displayed a significantly higher score than controls for all three mechanisms (attentional mechanism: $F = 28.16$, $p < 0.0001$; constructive mechanism: $F = 22.85$, $p < 0.0001$; deconstructive mechanism: $F = 37.69$, $p < 0.0001$).

Are differences in psycho-affective scores associated with brain changes through specific meditation mechanisms?

Which psycho-affective score does each meditation mechanism score preferentially impact?

To determine, for each meditation mechanism (attentional, constructive, and deconstructive), whether it exhibited a more pronounced influence on positive or negative psycho-affective scores, multiple linear regression models – using the adjusted r^2 and the standardized coefficient as a discriminating tool – and correlation coefficient comparisons, controlling for age, sex, and education, were conducted and results are reported in Tables 2 and 3 respectively. They revealed that the attentional mechanism score was more strongly associated with the positive ($\beta = 0.38$, $p < 0.0001$, $r^2 = 0.13$) than with the negative psycho-affective score ($\beta = -0.21$, $p = 0.007$, $r^2 = 0.08$). The constructive score also showed a significantly stronger correlation with the positive ($\beta = 0.43$, $p < 0.0001$, $r^2 = 0.16$) than the negative psycho-affective score ($\beta = -0.13$, $p = 0.10$, $r^2 = 0.05$). Finally,

	Positive psycho-affective score[1] ~ Attentional mechanism VS Negative psycho-affective score[1] ~ Attentional mechanism	**Positive psycho-affective score[1] ~ Constructive mechanism VS Negative psycho-affective score[1] ~ Constructive mechanism**	**Positive psycho-affective score[1] ~ Deconstructive mechanism VS Negative psycho-affective score[1] ~ Deconstructive mechanism**
Pearson and Filon's z (1898)	$z = 2.25$, $p = 0.012$	$z = 4.10$, $p < 0.0001$	$z = -2.21$, $p = 0.014$
Dunn and Clark's z (1969)	$z = 2.23$, $p = 0.012$	$z = 4.06$, $p < 0.0001$	$z = -2.23$, $p = 0.013$
Meng, Rosenthal, and Rubin's z (1992)	$z = 2.22$, $p = 0.013$	$z = 3.99$, $p < 0.0001$	$z = -2.22$, $p = 0.013$
Hittner, May, and Silver's z (2003)	$z = 2.22$, $p = 0.013$	$z = 4.02$, $p < 0.0001$	$z = -2.22$, $p = 0.013$

Table 3. Two by two correlation coefficient comparisons between meditation mechanisms and psycho-affective scores (with residuals). Comparisons of the correlation coefficients between the psycho-affective scores and each meditation mechanism (with residuals) were performed on R-studio. Statistical values were obtained after testing the alternative hypothesis "greater" for the attentional and constructive mechanisms and "less" for the deconstructive mechanism and were considered significant when $p < 0.05$. [1] Statistical values were obtained by comparing correlation coefficients between each meditation mechanism and the residuals of the multiple linear regressions between the psycho-affective scores and the covariates (age, sex and education).

the deconstructive mechanism score was more strongly correlated with the negative (β = -0.70, $p < 0.0001$, r^2 = 0.52) than the positive psycho-affective score (β = 0.60, $p < 0.0001$, $r^2 = 0.31$). When directly comparing the two correlation coefficients (Table 3), the difference was significant (attentional: $p = 0.012$; constructive $p < 0.0001$; deconstructive: $p = 0.013$). When adding the group (meditators *versus* controls) as a covariate, most results (from multiple regressions and correlation coefficient comparisons) remained similar (see Supplementary Tables S4-S5), except that the association between the attentional mechanism and the negative psycho-affective score was no longer significant. When assessed only within the group of meditators, the link between the attentional mechanism and the negative psycho-affective score was no longer significant while the relationship between the constructive mechanism and the negative psycho-affective score became significant (see Supplementary Table S6). Moreover, the comparison of the correlation coefficients revealed no significant differences anymore (see Supplementary Table S7).

Do specific meditation mechanisms mediate the links between brain changes and positive or negative psycho-affective scores?

To directly assess whether the associations between cerebral integrity and psycho-affective scores were mediated by the meditation mechanisms, we performed mediation analyses (first on the whole sample, then controlling for the group and finally, in the meditation experts only, see below). To focus on the most relevant models and avoid multiple testing, the mediations were performed considering only: (i) the psycho-affective score the most strongly associated with each meditation mechanism as identified in the previous set of analyses; and (ii) the brain regions the most predictive of each meditation mechanism (see Supplementary Table S8-S10). This led to the selection of six mediation models to be tested. Results are shown in Fig. 3 and direct and indirect effects are reported in Table 4. Overall, mediation analyses showed that the attentional mechanism mediated the relationship between the temporo-parietal perfusion and the positive psycho-affective score (Fig. 3, model 1: $p = 0.002$). The constructive mechanism mediated the relationship between the IFG volume and the positive psycho-affective score (Fig. 3, model 2: $p = 0.02$). The constructive mechanism also mediated the relationship between temporo-occipital perfusion and the positive psycho-affective score (Fig. 3, model 3: $p = 0.036$). On the other hand, the deconstructive mechanism mediated the relationship between temporo-occipital perfusion and the negative psycho-affective score (Fig. 3, model 4: $p < 0.0001$). The deconstructive mechanism also mediated the relationship between the OFC volume and the negative psycho-affective score (Fig. 3, model 6: $p = 0.048$).

When adding the group (expert, meditation-naive) as a covariate, or when assessed only within the group of meditators, mediation analyses were performed considering the same prerequisites so that 2 models were tested in both instances (see Supplementary, Fig. S1-S2 and Tables S11-S12). Overall, findings pointed to the same conclusion but were more restricted. Thus, when adding the group as a covariate, the attentional mechanism also mediated the relationship between brain changes and the positive psycho-affective score and the deconstructive

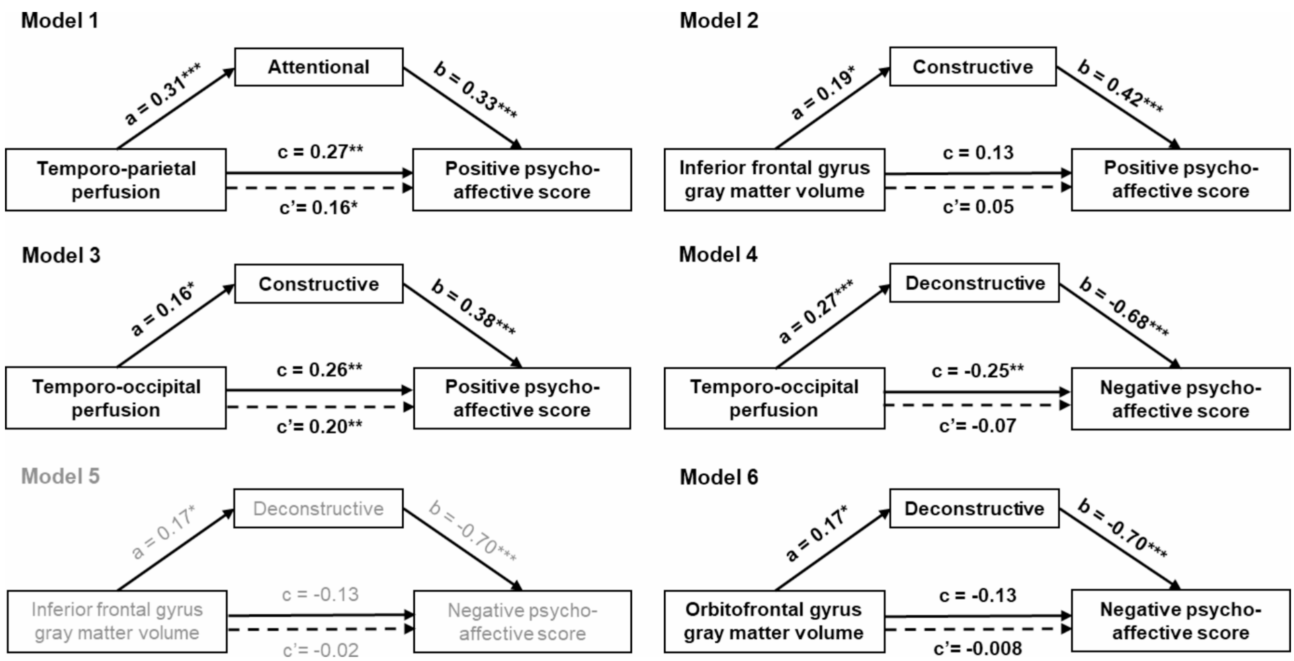


Fig. 3. Diagram of the mediation models illustrating the predictor (gray matter volume, perfusion), potential mediators (attentional, constructive and deconstructive mechanisms) and outcomes (positive and negative psycho-affective scores). Direct effects in filled arrows (simple regressions between variables) are expressed as standardized regression coefficients and indirect effects in dotted arrows (multiple regressions in which the predictor and the mediator are both added in the model) as partial correlation coefficients. Significant models are highlighted in bold black while the non-significant one is in gray. All regressions are adjusted for age, sex, and education. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

	ADE			ACME		
	Estimate	95% CI	*p* Value	Estimate	95% CI	*p* Value
Model 1	0.17	[0.01, 0.32]	0.04	0.11	[0.04, 0.20]	0.002
Model 2	0.05	[-0.08, 0.19]	0.47	0.08	[0.01, 0.16]	0.02
Model 3	0.21	[0.04, 0.37]	0.01	0.07	[0.01, 0.14]	0.036
Model 4	-0.07	[-0.18, 0.04]	0.26	-0.20	[-0.31, -0.08]	< 0.0001
Model 5	-0.02	[-0.13, 0.90]	0.76	-0.13	[-0.27, 0.01]	0.056
Model 6	-0.01	[-0.12, 0.12]	0.92	-0.13	[-0.24, 0.01]	0.048

Table 4. Detailed statistics of mediation analyses. Abbreviations: ADE = Average Direct Effect; ACME = Average Causal Mediation Effect; CI = Confidence Interval. In model 1, the temporo-parietal perfusion was entered as the independent variable while the IFG was included for models 2 and 5, the temporo-occipital region for models 3 and 4, and the OFC for model 6. The attentional mechanism was the mediator in model 1, the constructive mechanism was the mediator in models 2 and 3, and the deconstructive mechanism was the mediator in models 4, 5, and 6. Finally, in models 1, 2, and 3, the positive psycho-affective score was entered as the dependent variable while the negative psycho-affective score was included in models 4, 5, and 6. Statistics were estimated using non-parametric bootstrapping (x1000).

mechanism between brain changes and the negative psycho-affective score. When restricting the analyses to the meditators, only the mediation analysis with the constructive mechanism was recovered and it was also found to mediate the link between brain changes and the positive psycho-affective score.

Discussion

Our overall objective in this study was to address the mechanisms underlying meditation-related brain and psycho-affective changes in aging. As a first step, we aimed to identify the brain regions structurally and functionally preserved, and differences in positive and negative psycho-affective scores, in older expert meditators compared to older meditation-naive controls. Our findings revealed differences in the expected direction, with greater GMV and perfusion, as well as higher levels of positive and lower levels of negative psycho-affective scores, in the older expert meditators compared to controls. More specifically, we found brain differences (meditators > controls) occuring in the OFC, IFG and PCC for GMV and in the temporal, occipital, and parietal gyri for perfusion; while no difference was found in the opposite direction (controls > meditators). Overall, our findings are in agreement with the literature, as previous studies consistently found more preserved brain structure and function in expert meditators compared to controls in the context of older adult populations[26,29–33], although few studies focused on older adults. As for the specific brain regions, most of them are congruent with previous findings. Thus, the OFC, PCC, hippocampus, and inferior temporal gyrus are among the brain regions most commonly found to have a greater GMV in meditation practitioners[13,34]. The roles of these regions in cognition align with their involvement in meditation. For instance, the OFC is known for its role in emotion regulation[35], self-monitoring[36], and affective theory of mind[37]; the hippocampus in contextualized emotional learning towards producing adapted emotional responses[34]; and the inferior temporal gyrus in the mystical states associated with meditation[38,39]. The PCC is involved in self-referential processes[40,41] and theory of mind[42], supporting reflective self-awareness that meditation practices foster. While the PCC is also associated with mind-wandering[43], we propose that in expert meditators, this activity is characterized by intentional, adaptive self-reflection facilitating beneficial cognitive processes[44] rather than the ruminative, less productive thought patterns often associated with negative emotional outcomes. Previous studies reporting increased PCC volume in long-term meditators suggest that meditation enhances neuroplasticity in this region[47]. Given that our sample consists of older adults, this greater PCC volume is likely indicative of a preservation effect against age-related decline rather than an actual increase compared to the senior control group.

Other regions found here were more rarely highlighted in the meditation literature, but they could also be linked to meditation-related processes. Thus, involvement of the IFG could reflect its role in body awareness, interoception[45] and empathy as this structure is thought to be part of the mirror system involved in inferring other's emotions[46]. Findings in the occipital gyrus might reflect the fact that this structure supports mental imagery[47] which is used as a support in several meditation practices or exercises. The middle temporal gyrus is notably involved in cognitive reappraisal, interpreting actions, and reflecting on intentions, relevant to emotional reappraisal[48], also involved in meditation. Involvement of the superior temporal gyrus could be related to its role in insight in the context of problem solving[49] thought to be a core mechanism in meditation[15]. Finally, the insula was not found to be more preserved in the expert meditators in the present study while it was reported in a meta-analysis to be the most consistent finding in the literature assessing mindfulness-related changes in gray matter[50]. This difference might reflect the fact that the meta-analysis mostly included studies on young experts while we focused on older expert meditators that may still be susceptible to the structural effects of aging on this region.

While we found only greater GMV in older expert meditators compared to controls, it is important to note that greater volume does not always relate to a better outcome. For example, a study reported reductions in amygdala volume following mindfulness-based stress reduction, correlating with decreased stress levels[51]. However, the greater brain volume observed in older expert meditators here likely reflects a preservation effect against age-related decline rather than a straightforward increase in GMV. In the context of our findings, the preservation of brain volume suggests that meditation practices may promote healthy aging by counteracting the typical volume loss associated with aging.

Regarding the psycho-affective scores, we showed a higher level of positive psycho-affective score and a lower level of negative psycho-affective score in the older expert meditators compared to controls. These results are in line with the literature, meditation in older adults being associated with increased well-being[52], compassion, and emotion regulation as well as reduced stress, anxiety and depression[52] which are mostly included, respectively, in the positive *versus* negative psycho-affective scores used here.

As the next step, we aimed to identify the mechanisms underlying these brain and psycho-affective differences – focusing on the three main identified mechanisms from theoretical models namely attentional, constructive, and deconstructive capacities[14,15]. We found these capacities to be greater in meditators, consistent with our expectation as these composite scores were constructed to reflect skills trained by meditation[53].

Assessing the links between brain differences, meditation mechanisms and psycho-affective factors, we found, first, overall, that the brain regions showing greater preservation in older expert meditators were associated with improved psycho-affective factors (greater positive and reduced negative scores) through the three meditation mechanisms studied here. This result is in line with our global hypothesis and with the Medit-Ageing model. Second, in line with our expectations, we found the constructive mechanism to be more strongly associated with the positive than the negative psycho-affective score and to mediate the links between brain differences and the positive psycho-affective score; while the deconstructive mechanism preferentially linked to the negative psycho-affective score and mediated the links between brain and the negative psycho-affective differences. In contrast, our findings regarding the attentional mechanism being preferentially involved with the positive psycho-affective score are not in line with our hypotheses. These findings will be successively discussed in more detail below.

The constructive mechanism was shown to mediate the links between both, IFG volume and temporo-occipital perfusion, and the positive psycho-affective score. Both direct and indirect effects were significant, meaning that temporo-occipital perfusion predicted the psycho-affective score directly and through the constructive mechanism. The middle temporal gyrus present in the highlighted cluster has been associated with cognitive reappraisal[48], a core principle of the constructive mechanism[15]. Moreover, the impact of the constructive mechanism on the positive psycho-affective score was expected as this mechanism precisely aims to foster positive thoughts and emotions[14]. Note that this finding was observed in the meditators only, but not in the whole sample when adding the group as a covariate; this likely reflects the fact that the two groups showed a distinct relationship between the constructive mechanism and positive psycho-affective factors (a significant positive correlation in the meditators, *versus* a non-significant negative correlation in the controls). It seems that the constructive mechanism operates on upregulating positive psycho-affective factors only when duly trained (e.g. by meditation training) and not at the level of meditation-naive individuals.

The mediation effect of the constructive mechanism on the positive psycho-affective score was also observed with the IFG volume; yet only the indirect effect was significant, indicating that the link between this brain structure and the positive psycho-affective score only operates through improvement in the constructive mechanism. The link between the IFG and the constructive mechanism is consistent with the known role of this structure in empathy[46]. This result did not remain significant neither when adding the group as a covariate nor within the meditators. This might reflect the smaller sample size for the latter, or the fact that different degrees of expertise recruit different regions, i.e., that this relationship would be subtended by another brain region in expert meditators.

The deconstructive mechanism was shown to mediate the links between temporo-occipital perfusion and the negative psycho-affective score, with both direct and indirect effects being significant. Our findings suggest that perfusion of this brain region supports downregulation of negative psycho-affective factors, and that this process is reinforced by the deconstructive mechanism. The superior temporal gyrus – part of the temporo-occipital region – has be found to be associated with insight[49], which is thought to be one of the basis of the deconstructive mechanism[15]. In line with our hypothesis, as a mechanism centered around undoing maladaptive cognitive patterns[14], the deconstructive mechanism predominantly impacted the negative psycho-affective score. When adding the group as a covariate, this mediation remained significant (although a distinct brain region was entered in the model as the most linked to the deconstructive mechanism) while this mediation model was not tested in the meditators only given that no significant relationship was found between brain differences and the deconstructive mechanism.

The deconstructive mechanism was also found to mediate the link between the volume of the OFC and the negative psycho-affective score; yet only the indirect effect was significant indicating that the link between this brain structure and the negative psycho-affective score only operates through improvement in the deconstructive mechanism. The involvement of the OFC here is consistent with its role in self-monitoring[36], as the deconstructive mechanism notably relates to exploring one's self. Like the mediation involving the IFG, this result did not remain significant neither when adding the group as a covariate nor within the meditators, again possibly reflecting differences according to the level of expertise.

Finally, we found the attentional mechanism to mediate the relationship between temporo-parietal perfusion and the positive psycho-affective score, with both direct and indirect effects being significant. These results are consistent with the role of the parietal gyrus in attentional processes[54]. However, contrary to our hypothesis, the attentional mechanism predominantly impacted the positive psycho-affective score. We predicted that it would preferentially downregulate negative psycho-affective factors as this process is more specifically trained through MM practice, encouraging the development of mindful and non-reactive presence, the non-judgment observation of sensation and thoughts in the present moment. This neutral appraisal is, in turn, expected to downregulate negative psycho-affective factors. We indeed found a significant link between the attentional mechanism and the negative psycho-affective score. Yet, we did not anticipate that the attentional mechanism would have a stronger link with the positive psycho-affective score than the negative one. Nonetheless, we acknowledged that the different mechanisms are likely to interact and operate concomitantly on both psycho-affective processes. When adding the group as a covariate, the results remained the same, indicating that the role of attentional processes in the upregulation of positive psycho-affective factors is not conditioned by meditation expertise. Actually, this mediation was not recovered when restricting the analyses to the older expert meditators, but the results were in the same direction (the attention mechanism showed a greater link with the positive than the negative psycho-affective score).

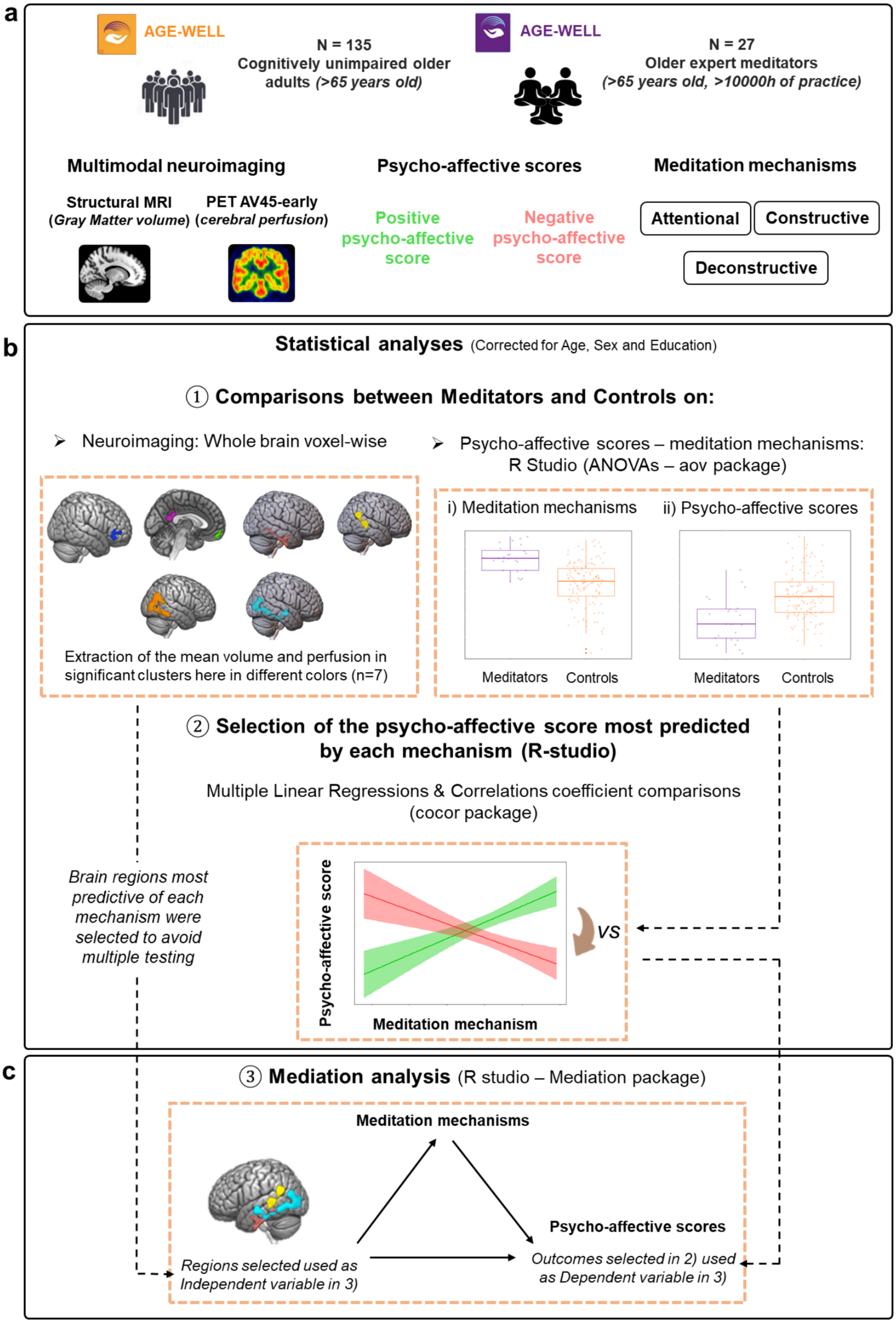
Although each mechanism was found to be preferentially associated with one psycho-affective score, they did correlate with the two of them, suggesting that these mechanisms are intertwined and interact together on both psycho-affective processes – which is in line with our hypothesis. Moreover, although these mechanisms reflect capacities existing in every individual and are acting together in both populations, they are more operative in older expert meditators as demonstrated by greater scores in all three mechanisms, as well as a higher positive psycho-affective score and a lower negative psycho-affective score in meditators compared to controls.

It is interesting to note that, when focusing on the meditators only, (i) the attentional mechanism was found to be the least associated to the psycho-affective processes, while the constructive and deconstructive mechanisms, associated to both psycho-affective processes, are respectively more involved in the positive *versus* negative psycho-affective score respectively; and (ii) the constructive mechanism is the only one remaining significant in the mediation analyses i.e., appears as the main mediator of the links between brain differences and psycho-affective scores. Moreover, the comparisons of the correlation coefficients between the mechanisms and the psycho-affective scores did not differ, suggesting that the mechanisms were particularly intertwined in this group; long-term use and proficiency in these mechanisms may foster their interaction in more complex and integrated meditation exercises and practices.

We made the hypothesis that the meditation mechanisms would mediate the links between meditation-induced brain differences and the psycho-affective scores. Yet, an alternative (and non-exclusive) hypothesis would be that meditation would impact the meditation mechanisms, which would then induce brain differences through the positive impact on the psycho-affective scores. We also tested for this hypothesis by conducting mediation analyses where the psycho-affective scores mediated the association between the meditation mechanisms and brain integrity (see Supplementary Table S13 and Fig. S3). Two mediation models (out of the 5 models tested) were statistically significant. They showed that the positive psycho-affective score mediated the relationship between both attentional and constructive mechanisms and brain perfusion. This suggests that the relationships between brain integrity and the psycho-affective scores could be bidirectional with brain differences subtending positive psycho-affective differences, which in turn could in term promote brain preservation. Further studies are needed to explore, longitudinally, the dynamic and directionality of these relationships.

The present study has strengths and limitations. The combination of several imaging modalities together with a set of psycho-affective scores allowing to assess positive and negative psycho-affective factors, and exploration of the three main putative meditation mechanisms, allowed to comprehensively assess the mechanisms relating meditation to brain and psycho-affective differences. To our knowledge, it is the first study exploring meditation mechanisms in aging. There are also very few studies focusing on expert meditators in the context of aging. Considering the scarcity of studies in older expert meditators and the difficulty in recruiting meditators in this age range to perform neuroimaging scans, the sample of meditators who underwent neuroimaging ($n = 25$) was relatively large in this study. Furthermore, we acknowledge the diversity of the meditation traditions represented, as the experts were trained in Zen, Theravada, and Tibetan Buddhism. While these traditions may emphasize different aspects of MM and LKCM, this diversity could enhance the generalizability of our findings by identifying common effects of meditation across these traditions. Given this variability, the construct of meditation expertise becomes particularly complex, as practice duration or reductions in positive or negative states may not be fully representative of meditation expertise. Meta-analyses have shown that experience itself is not a sufficient criteria to quantify such a construct[55,56], as it is not always a stronger predictor than a measure related to the domain of expertise[57]. Future studies should include multidimensional criteria to better represent meditation expertise. Moreover, in our study, the positive and negative psycho-affective factors measured were chosen for their relevance in reflecting enduring effects of meditation, thus serving as indicators of expertise. Specifically, the positive factor uses measures relevant to psychological resilience and brain reserve, which are stable indicators of psychological health. Conversely, the negative factors address common targets in meditation practices aimed at reducing psychological distress. Alternatively, these group differences may not be accounted only by meditation expertise but could reflect also individual difference preceding the meditation training[55,56]. Longitudinal designs are needed to address specifically this question and to infer causality between the variables tested here. Furthermore, despite having a larger sample size compared to other studies, our cohort of expert meditators remains relatively small. This constraint may have hindered our ability to detect certain effects of meditation within this group. We also highlighted weak mediation effects, maybe indicating that other processes not taken into account in the Medit-Ageing model are also at work here. Investigating other putative mechanisms in future studies would progressively allow us to get a more precise picture of the different active components of meditation. Another limitation is that the psycho-affective scores were constructed based on self-reported measures, which are inherently subjective. Additionally, they were computed by including available psycho-affective measures related to either positive or negative psychological processes but were not based on an *a priori* theoretical framework. Future studies, utilizing refined constructs for positive and negative psycho-affective composites based on a theoretical framework, and possibly including objective quantified measures, would provide further confirmation of our study and the Medit-Ageing model.

To sum up, long-term meditation promotes both structural and functional brain preservation in aging and improves psycho-affective factors. Attentional, constructive and deconstructive mechanisms relate to brain and psycho-affective differences, through specific effects on either positive or negative psycho-affective processes,



but also as interconnected mechanisms acting in concert on both psycho-affective factors. These exploratory findings shed light on the potential neurobiological and psychological mechanisms underlying the benefits of meditation in aging populations, providing insights to refine meditation interventions for better development of active components.

Material & Methods

Participants

We included 27 older expert meditators and 137 meditation-naive older adults from the baseline data of the Age-Well randomized clinical trial of the Medit-Ageing European Project[58,59] (Fig. 4a), sponsored by the French National Institute of Health and Medical Research (INSERM). Older expert meditators were recruited in Europe through flyers, advertisement in buddhist magazines, e-mails, and presentations in Buddhist meditation retreat

◀**Fig. 4**. Design overview. **a**. 27 older expert meditators and 135 older healthy meditation-naive controls underwent neuroimaging acquisitions for different modalities and filled self-reported measures that were used to construct composite scores reflecting psycho-affective scores and meditation mechanisms. **b**. (1) Whole brain voxel-wise comparisons were performed to assess the structural and functional brain regions better preserved in expert meditators compared to controls. Volume and perfusion values were then extracted from the regions highlighted for further analyses. Then, both populations were compared on their measures of psycho-affective scores and meditation mechanisms using ANCOVAs (aov package – R studio). (2) Multiple linear regressions were performed between each psycho-affective score (dependant variable) and each meditation mechanism (independent variable) to assess, for each meditation mechanism, whether it predominantly influenced one psycho-affective score over the other. **c**. Mediation analyses were performed based on the results of 2), and the selection of the brain regions that best predicted each mechanism, to assess whether the meditation mechanisms mediated the relationship between brain regions and psycho-affective scores.
Abbreviations: MRI Magnetic Resonance Imaging, PET Positron Emission Tomography; ANCOVA ANalysis of COVAriance.

centers (Supplementary Fig. S4). Older expert meditators had extensive practices in two families of Buddhist meditations: MM and LKCM and were trained in Zen, Theravada, or Tibetan Buddhism. To operationalize expertise, we required that experts have practiced these meditation types for a minimum of 10,000 h throughout their lifetime, maintained a regular practice schedule (at least 45 min per session, 6 days a week), and participated in meditation retreats totalling at least 6 cumulative months (i.e., at least 8 h of meditation per day). We combined these objective measures, with intersubjective criteria. Specifically, a research assistant with extensive experience in these practices conducted informal interviews with participants about their experience and knowledge. Whenever possible, the assistant also confirmed with participants' Buddhist communities that they were regarded as sufficiently skilled and experienced meditators (for details see Lutz et al. 2018)[59]. From the initial sample of 27 older expert meditators, two were excluded from the MRI analyses and 3 from the PET analyses (see Supplementary Fig. S4).

The meditation-naive controls were recruited from the general population, were all native French speakers, aged over 65 years old, educated for at least 7 years, and cognitively unimpaired (Supplementary Fig. S5). They had no evidence of major neurological or psychological disorders, no history of cerebrovascular disease, no chronic disease or acute unstable illness and no current medication that may interfere with cognitive functioning. Out of the 137 meditation-naive older adults, two were excluded from the trials and 3 additional controls were excluded from PET analyses (Supplementary Fig. S5).

Participants meeting inclusion criteria underwent a detailed cognitive and psychological assessment, blood tests, structural Magnetic Resonance Imaging (MRI), ^{18}F-fluorodesoxyglucose (FDG) and Florbetapir Positron Emission Tomography (PET) scans (Fig. 4a). All participants gave their written informed consent prior to the examinations, and the Age-Well Randomized Controlled Trial was approved by the ethics committee (CPP Nord-Ouest III; trial registration number: EudraCT: 2016-002441-36; IDRCB: 2016-A01767-44; ClinicalTrials.gov Identifier: NCT02977819). All experiments were performed in accordance with relevant guidelines and regulations.

Neuroimaging assessment

All participants included in the analyses were scanned on the same MRI (Philips Achieva; 3.0 T) and PET cameras (Discovery RX VCT 64 PET-CT; General Electric Healthcare) at the Cyceron Center (Caen, France).

MRI data acquisition and pre-processing

High-resolution T1-weighted structural imaging were acquired to measure GMV using a 3D fast-field echo sequence (3D-T1-FFE sagittal, repetition time = 7.1 ms, echo time = 3.3 ms, flip angle = 6°, 180 slices with no gap, slice thickness = 1 mm, field of view = 256 × 256 mm², in-plane resolution = 1 × 1 × 1 mm³). T1-weighted images were first segmented using multimodal segmentation (with Fluid Attenuated Inversion Recovery [FLAIR] images), then spatially normalized to the Montreal Neurological Institute (MNI) template, and modulated for nonlinear warping using the Segment function of SPM12. Resulting local GMV maps corrected for brain size were finally smoothed with a Gaussian kernel of 8 × 8 × 8 mm³ (x, y, z). Non smoothed images were also used to extract the individual GMV in both older expert meditators and older meditation-naive controls using a mask extracted from the analysis including regions in the frontal and parietal gyri.

PET data acquisition and pre-processing

Florbetapir scans were acquired with a resolution of 3.76 × 3.76 × 4.9 mm³ (field of view = 157 mm). Forty-seven planes were obtained with a voxel size of 1.95 × 1.95 × 3.27 mm³. A transmission scan was performed for attenuation correction before the PET acquisition. Each participant underwent a 4 min PET scan beginning 1 min after the intravenous injection of ~4MBq/Kg of Florbetapir, reflecting cerebral perfusion. PET data were co-registered onto their corresponding T1-weighted MRI, and normalized to the MNI template using the deformation parameters derived from the segmentation of the anatomical MRI. Resulting images were then scaled using the brainstem white matter as a reference. Normalized and scaled Florbetapir PET data were smoothed with a Gaussian kernel of 8 × 8 × 8 mm³ (x, y, z). Scaled Florbetapir PET images were also used to extract the individual standard uptake value ratio (SUVR) in both older expert meditators and older meditation-naive controls using a mask extracted from the analysis including the temporal, occipital, and parietal clusters.

Psychological assessment

The theoretical framework of the Medit-Ageing model proposes that meditation positive impact on aging operates through the downregulation of negative psycho-affective factors and the upregulation of positive ones[14]. As our goal here was to test this model, we constructed two composite scores reflecting positive *versus* negative psycho-affective factors. Each composite score was computed by (i) averaging the z-scores of the scales that were assigned to the respective psycho-affective composite score (Supplementary materials 1 & 2), using the mean and standard deviation of the entire control group; and (ii) dividing the averaged z-score by its standard deviation across the control group. The positive psycho-affective composite was computed by averaging the standardized scores of the Compassion for Self Short-form[60] (SCS-SF), the cognitive reappraisal subscale of the Emotion Regulation Questionnaire[61] (ERQ), the Satisfaction with life Questionnaire[62] and the Ryff 7 item Well-Being Scale[63]. The well-being, satisfaction with life and compassion for self scales allow us to assess global positive functioning and emotions as to reflect a positive psycho-affective state while reappraisal allows us to measure adaptive behavior/processes that has a positive impact on such functioning. A greater value would thus indicate a more positive psycho-affective state. The negative psycho-affective composite score was computed by averaging the standardized scores on the Death Depression Scale[64] (DDS), Penn-State Worry Questionnaire[65] (PSWQ), the Attentional Style Questionnaire[66] (ASQ) measuring distraction and concentration difficulties, the State-Trait Anxiety Inventory form A[67] (STAI-A) and the brooding subscale of the Rumination Response Scale (RRS)[68]. The DDS, STAI-A, PSWQ and brooding (RRS) scales allow us to measure factors that contribute to negative functioning and emotions while the distraction scale lets us measure detrimental behavior/processes that have a negative impact on such functioning and emotions. Scores in the Geriatric Depression Scale[69] (GDS, scores ranging from 0 to 15) and the Three-item Loneliness Scale[70] (scores ranging from 3 to 9) were not included in this negative psycho-affective score construct as they showed a marked floor effect. A greater value would thus indicate a more negative psycho-affective state. Detailed description of each scale and subscale used to construct the positive and negative psycho-affective composite scores are provided in the Supplementary materials.

Meditation mechanisms

The Medit-Ageing model posits that the upregulation of positive psycho-affective factors and downregulation of negative ones are subtended by 3 mechanisms (attentional, constructive, and deconstructive), inherent in all individuals and further refined through meditation practice. These three mechanisms are derived from the theoretical model introduced by Dahl et al. (2015), which is grounded in phenomenology and informed by a synthesis of the relevant literature in clinical psychology, cognitive neuroscience, and contemplative studies. Attentional, constructive, and deconstructive families can be understood as theory-based psychological mechanisms by which the practice of meditation is expected to exert its impact on well-being[15,71]. The meditation composite scores, derived from the theoretical framework encompassing these three mechanisms, have garnered some empirical validation[53,72]. To investigate these mechanisms, we used 3 composite scores using self-reported questionnaires that reflect the capacities manifested by each mechanism. Each composite score was computed by averaging the z-scores of the scales that were assigned to the respective composite[53]. A higher score indicates higher attentional, constructive or deconstructive capacities. The attentional mechanism score was not computed for 1 meditator and 1 control because of missing data at baseline on a subscale assigned to the attention regulation mechanism.

Statistical analysis

All following analyses were controlled for age, sex and education. First, we aimed to assess the differences in GMV and cerebral perfusion between older expert meditators and older meditation-naive controls. To that end, we performed voxel-wise two-sample t-tests in both structural MRI and early Florbetapir-PET using a threshold of p (cluster-level uncorrected) < 0.005 and a value of k determined by Monte-Carlo simulation using the 3dClustSim program (AFNI 18.0.11) to achieve a corrected statistical significance of $p < 0.05$. Since this analysis was exploratory, we reported results using uncorrected p-values where FWE-corrected significance was not achieved. This approach allows for the detection of potentially relevant trends, acknowledging that while FWE correction is necessary for controlling false positives, its stringency may obscure meaningful differences, particularly in smaller sample studies. For further analyses, bilateral clusters were concatenated. We then extracted from the pre-processed images the average values of GMV and cerebral perfusion in the significant clusters of the previous analyses in the 135 controls and 25 meditators, to be used in later analyses (Fig. 4b).

Group comparisons analyses were also conducted on measures of meditation mechanisms and psycho-affective composite scores, using parametric analyses of covariance (ANCOVAs). Differences were considered as significant when $p < 0.05$. Bonferroni correction was applied to correct for multiple comparisons (Fig. 4b).

Then we aimed to assess whether each meditation mechanism predominantly influenced positive or negative psycho-affective scores. For this purpose, we performed multiple linear regressions with each meditation mechanism as the independent variable and each psycho-affective score as the dependant variable. We selected the psycho-affective score the most influenced by each meditation mechanism based on the standardized β as well as the adjusted R squared of each model. We also used the 'cocor' function to directly compare, statistically, the strength of the correlation with positive *versus* negative psycho-affective scores. As the 'cocor' function does not allow the inclusion of covariates, this model was applied to the residuals from the linear association between psycho-affective scores and age, sex, and education (Fig. 4b).

Then we aimed to investigate whether and which meditation mechanisms mediated the links between brain and psycho-affective differences with mediation analyses. To avoid multiple testing, we focused on the most relevant models considering only: (i) the psycho-affective score the most strongly associated with each meditation mechanism as identified in the previous analyses; and (ii) the brain regions the most predictive of each meditation mechanism. Forward stepwise regression analyses were conducted to select, for each meditation mechanism, the most predictive GMV or perfusion brain region(s). The best model was selected based upon the Akaike Information Criteria, a lower value indicating a better fit. The regressions were considered significant if $p < 0.05$. These regression analyses were performed using the "step" function of the "stats" package in R (R Core Team, 2019).

Then mediation analyses were conducted including the relevant pairs of mechanism-psycho-affective score and brain region-mechanism as determined from the previous analyses. We tested the mediation effects using the 'mediate' function of the "mediation" package[73] and reported the average direct effects and average causal mediation effects estimated using nonparametric bootstrapping based on 1,000 bootstrap samples ($p < 0.05$) (Fig. 4c).

Meditation mechanism scores are thought to reflect qualities that are inherent in all individuals to varying degrees, and that are further developed in meditation experts as these capacities are specifically trained by meditation practice. For this reason, all these analyses were first conducted throughout the meditation-naive and expert meditators older adult populations, controlling for age, sex and education. Secondly, to ensure that the links did not merely reflect the concomitant effect of meditation expertise on both measures, the same analyses were repeated while also controlling for the group (meditators vs. controls). Finally, because some relationships may only arise in the meditators as a reflection of long-term practice, the analyses were repeated within the group of older expert meditators. These 2 last analyses are reported in the Supplementary section.

Data availability

Data is available on request following a formal data sharing agreement and approval by the consortium and executive committee. The data sharing request form can be downloaded at https://silversantestudy.eu/2020/09/25/data-sharing/.

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Author contributions
GC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: SH, AL, and GC. Acquisition, analysis, or interpretation of data: SH, BL, FM, AL, and GC. Drafting of the manuscript: SH and GC. Critical revision of the manuscript for important intellectual content: SH, AL, BL, FM, MD, OH, NLM, OK, FC, JG, VDLS, DV, AL, and GC. Statistical analysis: SH. Obtained funding: SH, AL, NLM, OK, FC, JG, and GC. Administrative, technical, or material support: BL, FM, OH, and MD. Supervision: GC. Other—principal investigators: GC, VDLS (MD, principal investigator).

Declarations

Competing interests
The authors declare no competing interests.

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