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Mindfulness intervention for mild cognitive impairment led to attention-related improvements and neuroplastic changes: Results from a 9-month randomized control trial

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ABSTRACT

Mindfulness-based interventions can enhance cognitive abilities among older adults, thereby effectively delaying cognitive decline. These cognitive enhancements are theorized to accompany neuroplastic changes in the brain. However, this mindfulness-associated neuroplasticity has yet to be documented adequately. A randomized controlled trial was carried out among participants with mild cognitive impairment (MCI) to examine the effects of a mindfulness-based intervention on various cognitive outcomes and cortical thickness (CT) in the context of age-related cognitive impairment. Participants were assigned to a mindfulness awareness program (MAP)(n = 27) and an active control condition — health education program (n = 27). In both, they attended weekly sessions for three months and subsequently, monthly sessions for six months. Cognitive assessments and structural scans were carried out across three time-points. Whole brain analyses on CT were carried out and were supplemented with region of interest-based analyses. ROI values and cognitive outcomes were analyzed with mixed MANOVAs and followed up with univariate ANOVAs. Nine-month MAP-associated gains in working memory span and divided attention, along with an increased CT in the right frontal pole and decreased CT in the left anterior cingulate were observed. Three-month MAP-associated CT increase was observed in the left inferior temporal gyrus but did not sustain thereafter. MAP led to significant cognitive gains and various CT changes. Most of these neurobehavioral changes, may require sustained effort across nine months, albeit at a reduced intensity. MAP can remediate certain cognitive impairments and engender neuroplastic effects even among those with MCI.

1. Introduction

Early treatment in dementia is crucial to maximizing treatment outcomes and functional independence (Gauthier, 2005). To this end, the mild cognitive impairment (MCI) diagnostic entity conceptualized two decades ago, has been positioned as the intermediate stage between

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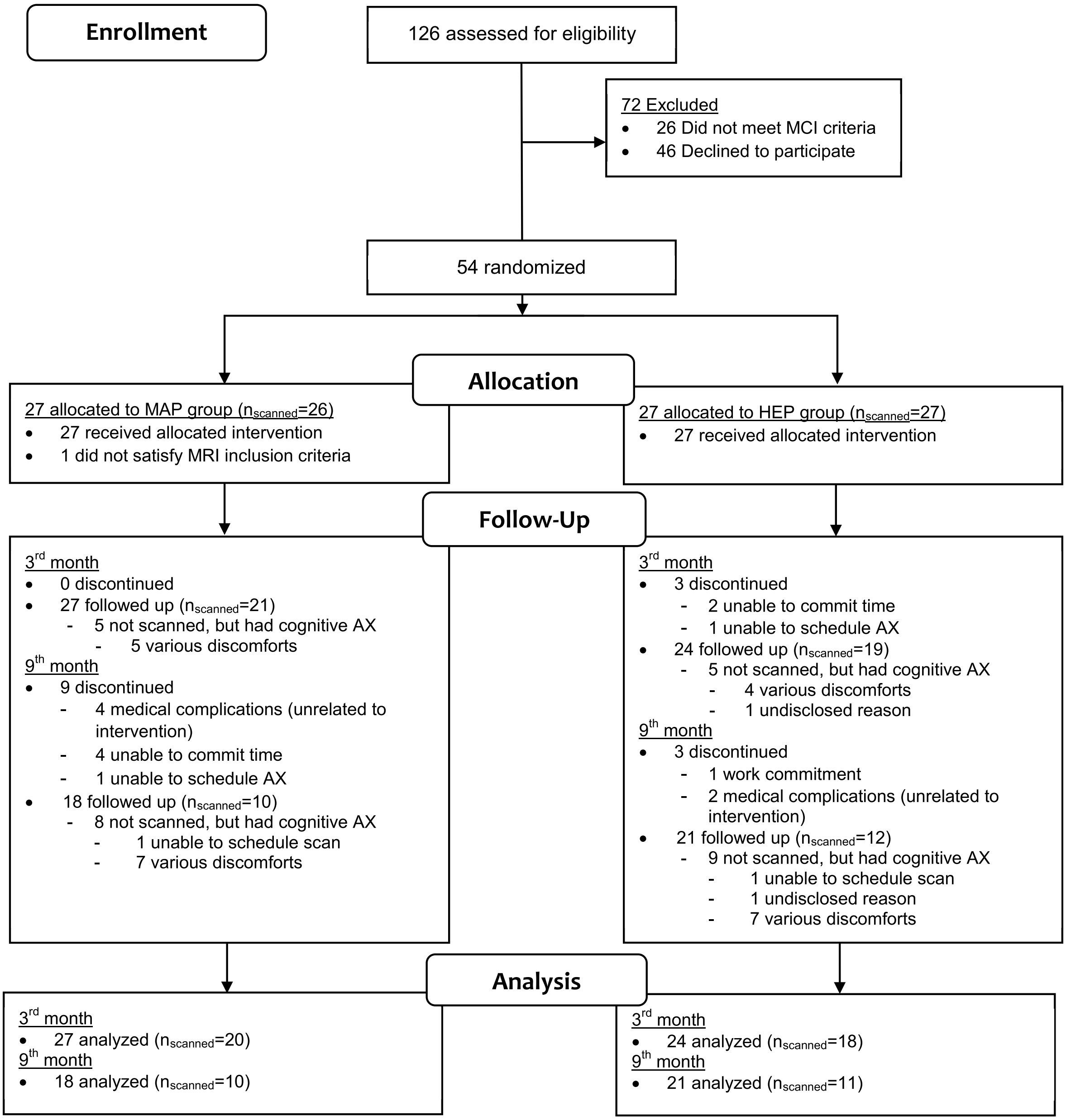

Fig. 1. Consort flow diagram. MCI = mild cognitive impairment; MRI = magnetic resonance imaging; MAP = Mindfulness Awareness Program; HEP = Health Education Program; AX = assessment.

healthy aging and dementia, in which researchers are optimistic that interventions would alter the course of subsequent cognitive decline (Petersen et al., 2014).

Among the non-pharmacological interventions that have been carried out on the MCI population, there has been a growing interest in mindfulness-based interventions (Chan et al., 2019). Although such interventions traditionally target psychoaffective or behavioral issues (Baer, 2003), evidence suggests that they can bring about a strong cognitive enhancement effect (Chiesa et al., 2011) as well— which can be exploited to delay subsequent cognitive decline. This is due to the fact that meditation recruits several cognitive processes, which are trained upon repeated sessions.

Mindfulness meditation generally involves focused attention and/or open monitoring. In focused attention, the meditator has to direct and sustain attention on an internal or external stimulus for a period of time. In doing so, the meditator needs to constantly monitor his/her thoughts to detect mind wandering. Occasionally, the meditator disengages from a distracting object (attention switching) and redirects attention to another stimulus (selective attention)(Lutz et al., 2008). During open monitoring, the meditator attends to the moment-by-moment experience in the 'here and now' in a nonjudgmental manner. In doing so, he/she has to inhibit automatic cognitive appraisals and divert attention away from distracting stimuli that would obscure attention to the moment-by-moment experience (Jha et al., 2019). Essentially, meditation can be thought of as a type of cognitive training for these different cognitive abilities.

Alongside these training-related improvements, repeated sessions of meditation may also trigger experience-dependent neuroplastic changes. In this regard, one randomized controlled trial (RCT) assigned healthy participants (i.e., self-reported to be psychologically and physically healthy, and not taking any medications) to a nine-session Mindfulness-Based Stress Reduction (MBSR n = 16) intervention or a wait-list control condition (n = 17) and compared the gray matter (GM) changes between both groups. It was observed that the GM volumes in

Table 1
Characteristics of participants assigned to both treatment conditions.

	MAP (N = 27)	HEP (N = 27)	Between-group comparison		
			t	χ^2	p
Mean age (SD)	71.3 (5.6)	71.4 (6.0)	.12		.91
Sex					
Male	8	6		.39	.54
Female	19	21			
Mean years of education (SD)	5.2 (4.9)	3.4 (4.3)	1.39		.17
Mean MMSE score (SD)	24.6 (3.3)	24.7 (3.9)	.11		.91
Mean sessions attended[a] (SD)					
First 3 months (12 sessions)	10.6 (1.5)	10.8 (1.4)	.30		.77
Subsequent 6 months (6 sessions)	5.2 (1.5)	5.3 (1.2)	.9		.93

Note. MAP = Mindfulness awareness program; HEP = Health education program; SD = standard deviation; MMSE = Mini-Mental State Examination.
[a]Among the analyzed longitudinal sample.

Table 2
Cognitive outcomes assessed.

Test	Outcomes	Cognitive functions assessed
Semantic fluency test	Number of unique animals	Verbal fluency
Color trails test	Interference effect	Divided attention and set-switching
Digit span subtests (WAIS-III)	Digits forward total score	Working memory span
	Digits backward total score	Working memory manipulation
Rey Auditory Verbal Learning Test	Immediate recall	Immediate memory
	Delayed recall	Delayed memory
	Delayed recognition	Recognition memory
Block design test (WAIS-III)	Total raw score	Visuospatial processing

Note. WAIS-III = Wechsler Adult Intelligence Scale III.

left posterior cingulate cortex, left temporo-parietal junction, hippocampus and bilateral regions in the cerebellum had increased in the MBSR group as compared to the wait-list controls (Hölzel et al., 2011). Another RCT (Pickut et al., 2013) compared 14 patients with Parkinson's disease assigned to an eight-week mindfulness-based intervention and 13 patients on usual care, and found increased GM volume in the bilateral caudate nucleus, left occipital lobe, left thalamus and bilateral temporo-parietal junction in the former group. A third RCT compared 12 college students assigned to a 4-week Sahaja Yoga meditation training with 30 wait-list controls and found meditation-associated GM increase in the right inferior frontal gyrus (Dodich et al., 2019). Additionally, two other RCTs (Tang et al., 2010; Wells et al., 2013) did not observe significant meditation-associated GM changes. In general, the evidence on the neuroplastic GM changes associated with meditation has been limited and inconclusive.

In addition to replicating the previously documented meditation-associated cognitive gains, we sought to make a meaningful contribution to the limited pool of evidence relating to the meditation-associated neuroplasticity. The current study evaluates the effect of a mindfulness-based intervention on various cognitive outcomes and GM cortical thickness (CT) across a 9-month intervention period. We hypothesized that such intervention would engender significant cognitive gains, especially in the attentional domains, as well as increase CT in various cortical GM regions which were found to differ between experienced meditators and meditation-naïve controls.

2. Material and methods

2.1. Design

The study was carried out as an open-label RCT. Randomization was stratified by gender and carried out in blocks of four using the Random Allocation Software 2.0 by an independent researcher. The intervention consisted of two arms— mindfulness awareness program (MAP) and health education program (HEP). The latter was used as an active control condition for the former, to control for possible effects due to social interaction. The intervention spans across nine months and consisted of two phases in both arms. During the first 3-month phase, sessions were held once per week for 12 sessions. Thereafter, these sessions took place once per month in the subsequent 6-month phase. The rationale for dividing the intervention into two different phases of different treatment intensities was to assess if the treatment gains from the first phase can be sustained with much less time commitment from the participants in the second phase. Each session would last for 45 min. The CONSORT flow diagram of the study is shown in Fig. 1. Ethical approval for the current study was granted by a university's institutional research board.

2.2. Participants

Participants of the current study were recruited from the community, as part of the larger Aging in a Community Environment Study cohort (Feng, 2015). Details regarding the recruitment, which was carried out from 2011 to 2016 have been described elsewhere (Yu et al., 2016). Subsequently, participants from this cohort were invited to participate in the current intervention study. The inclusion criteria were 1) aged between 60 and 85 (inclusive), 2) met the criteria for mild cognitive impairment (MCI), 3) able to travel to the intervention venue independently, 4) not presenting with any current psychiatric or neurological conditions, 5) not suffering from any terminal illness, 6) not participating in another interventional study and 7) for those undergoing magnetic resonance imaging (MRI) scans, not having any metallic body implants (e.g., pacemaker), with the exception of dental implants.

The Petersen's (2004) criteria were used for the MCI diagnosis. These include subjective cognitive complaints as corroborated by a reliable informant, presence of objective cognitive impairment and largely preserved functional independence. In particular, the objective cognitive impairment criterion was operationalized as scoring 1.5 standard deviations (SD) below the age and education appropriate norms in any of six cognitive domains, as assessed via the digit span backward and block design tests from Wechsler Adult Intelligence Scale (WAIS-III), delayed recall and recognition tests from the Rey Auditory Verbal Learning Test (RAVLT), Color Trails Test (CTT), and semantic fluency test. The MCI diagnoses were made via a consensus from a panel of psychiatrists and psychologists.

Fifty-four participants were randomized into the two treatment conditions. Information regarding their demographic characteristics, general cognitive status and attendance are presented in Table 1. Independent samples t-tests suggest that both intervention groups were not significantly different in terms of attendance in the two phases (*ps* $\geq$ .77). Written informed consent was obtained from these participants prior to their participation. Among them, 51 had at least completed the first 3-month phase and 39 completed both phases. For the first three months, our calculations using G*Power indicated that the valid sample size would provide a power of 0.80 (assuming an alpha level of 0.05 and a 0.5 correlation between repeated measures) to detect a significant Time * Group interaction if the true effect was at least 0.40 SD. Across the entire 9-month intervention period, our calculations using the same parameters suggest that we can detect a true effect of at least 0.46 SD. Considering that a recent meta-analysis (Chan et al., 2019) revealed a much larger effect of meditation on global cognition among older adults (SMD = 0.56), our sample sizes are more than adequate to detect the hypothesized interaction effect on cognitive outcomes.

Table 3
Results of the mixed ANOVA on cognitive outcomes from baseline to ninth month.

Cognitive outcome	Time		Group		Time * Group			
	F	p	F	p	F	p	q	$\eta^2_{partial}$
Digit span forward	3.50	0.069	0.01	0.914	8.01	0.007	0.060	0.18
Digit span backward	0.61	0.438	0.90	0.348	1.85	0.182	0.484	0.05
Immediate recall	7.00	0.012	3.65	0.064	0.40	0.533	0.849	0.01
Delayed recall	10.48	0.003	3.87	0.057	0.09	0.770	0.849	<.01
Recognition	<.01	0.960	2.72	0.107	0.04	0.849	0.849	<.01
CTT - interference	1.58	0.217	3.03	0.091	5.03	0.031	0.126	0.13
Block design	11.17	0.002	2.27	0.140	0.28	0.600	0.849	<.01
Semantic fluency	0.91	0.348	0.47	0.495	0.12	0.732	0.849	<.01

Note. CTT = Color trails test; q = p values adjusted for false discovery rate.

2.3. Measures

Eight cognitive outcomes, indexing working memory span and manipulation, divided attention, immediate, delayed and recognition memory, verbal fluency and visuospatial processing from various tests were administered (see Table 2). The procedures for these tests are described in detail in the supplementary materials. For these measures, higher scores correspond to better performance, with the exception of the CTT interference, in which smaller interference scores relate to better performance.

2.4. Intervention protocol

The MAP was modeled on similar group-based mindfulness meditation for older adults (McBee, 2008) and was led by an experienced instructor. Participants were taught 1) mindfulness of the senses practice— to attend to the different senses (i.e., vision, hearing, touch) to cultivate focused attention; 2) body scan practice— to develop kinesthesia by focusing their attention on various parts of their body as a relaxation technique, while in a sitting and/or supine position; 3) walking meditation practice— to cultivate calmness and momentary concentration by walking slowly with mindfulness; 4) 'movement nature meant' practice— to move with awareness for flexibility, strength and confidence; and 5) visuomotor limb tasks that train one's mind-body coordination.

The weekly HEP didactic sessions were taught by an experienced instructor, and covered topics such as chronic medical conditions (e.g., hypertension, diabetes, arthritis), medication compliance, and healthy lifestyles (e.g., diet, nutrition, exercise, and relaxation). In the subsequent monthly discussion sessions, participants shared how they had applied what they learned to their daily lives. Both programs were separately carried out in a quiet room in a community location.

2.5. MRI acquisition

Participants were scanned in a 3-T Siemens Tim Trio scanner at the Clinical Imaging Research Center, Singapore. T1-weighted images were acquired using an MPRAGE protocol (TE = 1.90s; TR = 2.30s; TI = 900 ms; 256 × 256 matrix; 192 sagittal slices; in-plane resolution = 1 mm; slice thickness = 1 mm).

2.6. Image preprocessing

T1-weighted images were preprocessed longitudinally using the CAT12 (version r1450) as implemented in SPM12 (version 6225) within MATLAB (R2019a). Baseline and follow-up images were rigidly realigned within-subject to correct for differences in head position and a subject-specific average template was computed and used as reference in a subsequent realignment of the baseline and follow-up images. The realigned images were segmented into GM, white matter (WM) and cerebrospinal fluid, as well as corrected for signal inhomogeneities with reference to the subject average template. These GM and WM images were used to estimate spatial normalization deformation fields using the high dimensional Diffeomorphic Anatomic Registration Through Exponentiated Lie Algebra (DARTEL) warping algorithm (Ashburner, 2007) which were applied to segmented images and subsequently modulated. These modulated images were then visually inspected.

Estimation of CT and the central surface was carried out using the projection-based thickness method (Dahnke et al., 2013), which consisted of topology correction (Yotter et al., 2011), spherical mapping, and spherical registration (Yotter et al., 2011). After obtaining the segmented images, WM distance was estimated and the local maxima were projected to other GM voxels using a neighbor relationship described by the WM distance (Dahnke et al., 2013). The 'surface thickness and thickness estimation for ROI' writing option was used to extract region-of-interest (ROI) values from the Desikan-Killiany atlas (Desikan et al., 2006).

2.7. Statistical analyses

We were primarily interested in the treatment gains at the two possible 'exit points' —third and ninth month, hence for the following analyses we compared the outcomes between baseline and third month, as well as between baseline and ninth month timepoints.

First, we carried out whole brain analysis on the preprocessed surfaced images. Two subjects (one from each treatment group) were excluded from these analyses due to significant lesions. Then, treatment effects were assessed using a flexible factorial GLM, modeling the three factors of Subject, Group and Time, in which we examined the T contrasts for the Group * Time interaction (i.e., $\text{Time}_{post} > \text{Time}_{pre}$ & MAP > HEP and $\text{Time}_{post} > \text{Time}_{pre}$ & MAP < HEP). The results were thresholded using $p < 0.05$, family-wise error (FWE) correction against a null-distribution generated by 5000 nonparametric permutations using the TFCE toolbox, with a cluster extent threshold of $k > 20$. Significant clusters are labeled using the Desikan-Killiany atlas.

Given the relatively small number of scanned participants, a whole brain analysis was unlikely to yield multiple clusters that would survive the stringent FWE corrections. Hence, we supplemented the whole brain analyses with ROI-based analyses. Specifically, we selected on an a priori basis, ROIs that corresponded to the significant cortical GM clusters identified in a meta-analysis that compared between experienced meditators and meditation naïve controls (Fox et al., 2014). These included the bilateral regions of the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), frontal pole (FP) and insula. Apart from the first two, these ROIs were extracted as they were parcellated in the atlas. The ACC ROI was created by summing the caudal and rostral anterior cingulate ROIs, and the OFC ROI was created by summing the lateral and medial orbitofrontal ROIs. These ROIs were entered into subsequent analyses together with the cognitive outcomes.

For the analyses of the cognitive outcomes and CT ROIs, in order to minimize the false positive results associated with multiple testing, multivariate analyses of variance (MANOVA) were carried out separately on the cognitive outcomes and CT ROIs, with time and group as the within- and between-subject factors, respectively, to determine the

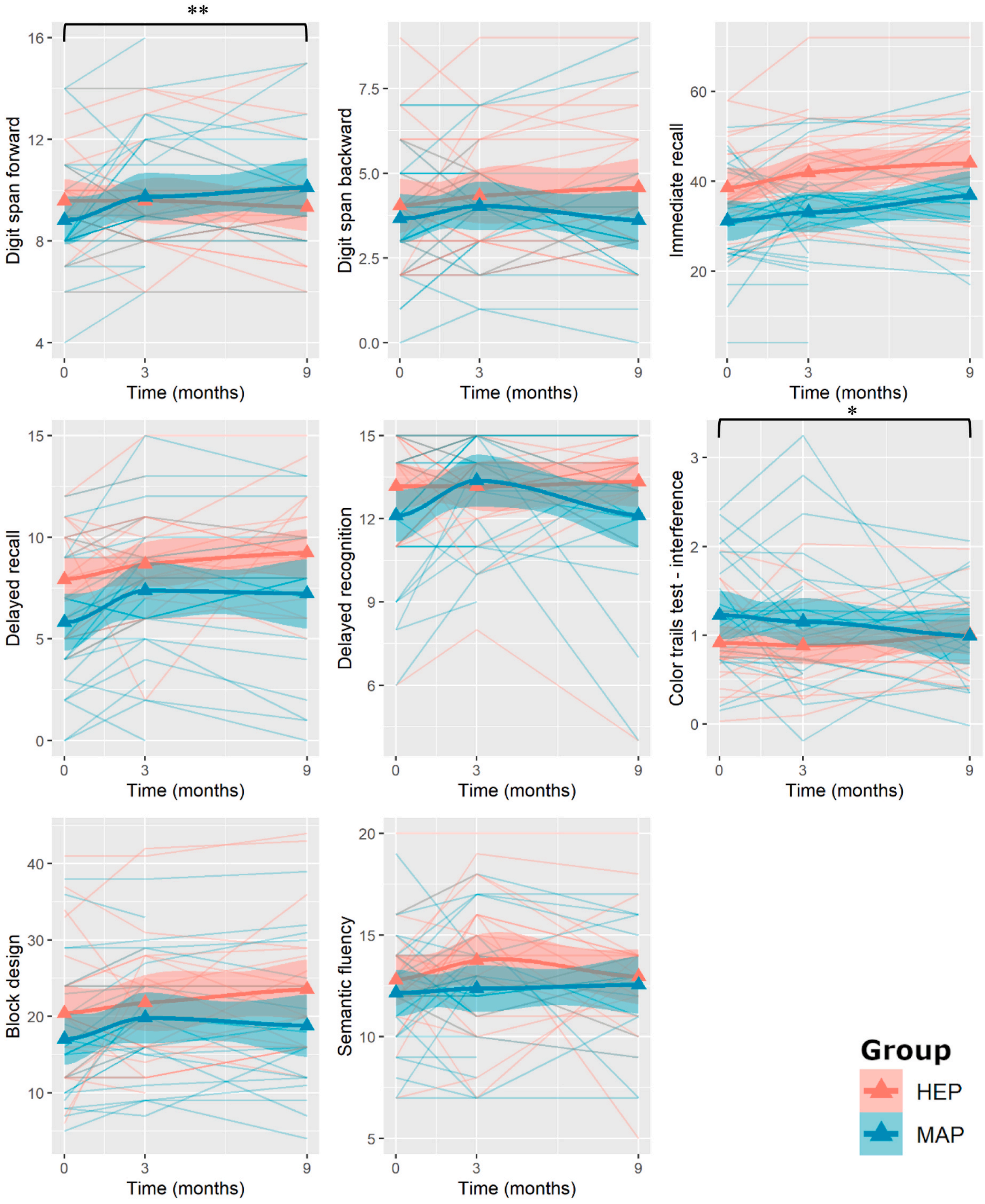

Fig. 2. Trajectories of cognitive outcomes in each group across time. The thick colored lines represent the mean trajectory of each group, which are enclosed within their respective 95% confidence intervals. *p < .05; **p < .01.

overall effect on the assessed outcomes. In line with our general analytical framework, the MANOVAs compared between baseline and third month, as well as between baseline and ninth month timepoints. If significant group*time interaction effects were obtained in any of these MANOVAs, post hoc univariate analyses of variance (ANOVA) were carried out individually on each outcome between the respective timepoints. Although it is possible to analyze all three timepoints in a single MANOVA and proceed with post hoc analyses, we did not do so. This is because the valid sample size at the ninth month timepoint is much smaller, given that the three-timepoint MANOVA can only be carried out on participants with valid data on all three timepoints, such analyses would discard several participants with incomplete ninth month data, ultimately reducing statistical power. Effect sizes for the significant statistics relating to the time * group interactions were quantified using partial eta square ($\eta^2_{partial}$), where $\eta^2_{partial}$ of 0.06 and 0.13 indicates medium and large effect sizes, respectively. Statistical significance was set at $p < .05$. For the post-hoc ANOVAs, we have additionally computed p-values adjusted for false discovery rate (FDR). Nevertheless, we do not expect the significant results of these ANOVAs to survive such corrections, as this would require very large treatment effects and sample sizes

Table 4
Results of the mixed ANOVA on the regions-of-interest from baseline to ninth month.

Regions-of-interest	Time		Group		Time * Group			
	F	p	F	p	F	p	q	$\eta^2_{partial}$
Anterior cingulate L	0.20	0.658	0.13	0.718	5.18	0.035	0.138	0.21
Anterior cingulate R	0.01	0.924	0.01	0.913	0.01	0.921	0.921	<.01
Orbitofrontal L	0.52	0.479	0.02	0.898	0.04	0.848	0.921	<.01
Orbitofrontal R	0.91	0.351	0.11	0.747	0.80	0.381	0.844	0.04
Frontal pole L	0.92	0.349	0.68	0.419	0.03	0.855	0.921	<.01
Frontal pole R	0.15	0.704	0.01	0.936	5.18	0.035	0.138	0.21
Insula L	1.63	0.217	0.08	0.784	0.16	0.695	0.921	<.01
Insula R	3.44	0.079	0.22	0.647	0.67	0.422	0.844	0.03

Note. L = Left; R = Right; q = p values adjusted for false discovery rate.

that are beyond what is expected or practical for this study. These analyses were carried out R 4.0.2. The R code for executing these analyses and generating the figures are available at https://osf.io/ykz2c/files/.

3. Results

3.1. Effect of MAP on cognitive outcomes

The MANOVAs revealed a significant Time * Group effect on cognitive outcomes between the baseline and ninth month ($F(8, 28) = 1.92$; $p = .022$; $\eta^2_{partial} = 0.44$),but not between baseline and third month ($F(8, 39) = 1.92$; $p = .106$; $\eta^2_{partial} = 0.27$). Thus, univariate ANOVAs were carried out to follow up on the significant effects between the baseline and ninth month. The detailed results of all modeled effects in these ANOVAs are presented in Table 3. In these post hoc analyses, significant Time*Group interactions emerged for digit span forward and CTT interference. Fig. 2 showed that the digit span forward score and CTT interference among MAP participants had increased and decreased, respectively over time, relative to their HEP counterparts. As expected, none of these significant post-hoc results survived the FDR correction.

3.2. Effect of MAP on cortical thickness

The MANOVAs on the CT revealed a significant Time * Group effect between baseline and ninth month ($F(8, 12) = 3.03$; $p = .041$; $\eta^2_{partial} = 0.67$), but not between baseline and third month ($F(8, 29) = 2.01$; $p = .080$; $\eta^2_{partial} = 0.36$). Univariate ANOVAs were carried out to follow up on the significant effects between baseline and ninth month. The detailed results of all modeled effects in these ANOVAs are presented in Table 4.These ANOVAs revealed a significant Time * Group on the right FP ($F(1, 19) = 5.19$; $p = .035$; $\eta^2_{partial} = 0.21$) and left ACC ($F(1, 19) = 5.18$; $p = .035$; $\eta^2_{partial} = 0.21$). Fig. 3 showed that, relative to HEP participants, the CT in the right FP and left ACC among MAP participants had increased and decreased, respectively, across this period. None of these significant post-hoc results survived the FDR correction. Additionally, none of the CT changes in any ROIs were significantly correlated with any of the changes in cognitive outcomes. The descriptive statistics of the ROI CT values across the three time-points are reported in the supplementary materials (see table S2).

Next, CT was analyzed at the whole brain level. Across the first three months, whole brain analyses within the contrast of $\text{Time}_{\text{3-month}} > \text{Time}_{\text{baseline}}$ & MAP > HEP revealed a significant cluster in the left inferior temporal gyrus (ITG)($k = 28$, peak level FWE-corrected $p = .009$; MNI = −55, −33, −24; see Fig. 4a). No significant clusters emerged in the reverse contrast (i.e., $\text{Time}_{\text{3-month}} > \text{Time}_{\text{baseline}}$ & MAP < HEP). Across the entire 9-month intervention period, no significant clusters were observed in any of the interaction contrasts. The uncorrected statistical maps of these contrasts are presented in the supplementary materials (see figures S1 and S2). Given these results, there is a possibility that the significant cluster obtained from the first 3-month period did not appear in the subsequent 6-month period, merely due to the reduced sample size. Hence, we investigated this further by extracting the significant cluster as an ROI and entering these ROI values into a mixed ANOVA. The Time * Group effect across the entire 9-month intervention period was not significant ($F(1, 36) = 0.21$; $p = .649$; $\eta^2_{partial} = 0.01$ see Fig. 4b), in contrast to the significant interaction across the first three months ($F(1, 19) = 23.27$; $p < .001$; $\eta^2_{partial} = 0.39$).

4. Discussion

The current study examined the effects of a mindfulness-based intervention on cognitive outcomes and CT. In the cognitive domain, we observed a gradual improvement in working memory span and divided attention among MAP participants relative to their HEP counterparts, culminating in medium to large effect sizes across the entire 9-month intervention period. As for CT, MAP participants, relative to their HEP counterparts had significantly increased CT, as quantified by a large effect size, in the right FP across the entire 9-month intervention period. At the end of the first 3-month phase, the CT in MAP participants had significantly increased in a left ITG cluster, as quantified by a large effect size, relative to HEP participants. However, these 3-month MAP-associated CT changes in the left ITG did not sustain until the ninth month. Overall, these results suggest that the MAP intervention led to significant cognitive gains and neuroplastic changes across the 9-month intervention period.

With repeated sessions of meditation, our MAP participants trained their abilities to engage and disengage their attention on various stimuli. Naturally, the effect of such attentional training would transfer to our measure of divided attention, where participants had to repeatedly engage and disengage between two sets of stimuli (i.e., pink and yellow circles in the CTT). Furthermore, we observed MAP-associated working memory improvements as measured by the digit span forward. Generally, working memory span benefits from an improved attention. A larger working memory span can be the result of a greater ability to control attention to avoid distraction and thereby maintain more stored items (Engle, 2002). Such controlled attention was practiced in our MAP as participants focused and sustained their attention on various external and interoceptive stimuli. However, we did not observe a similar MAP-associated improvement for working memory manipulation as measured by the digit span backward. Although meditation typically involves the manipulation information in the working memory, such manipulation is largely restricted to the engagement and disengagement of information in the present moment without judgment or elaboration (Jha et al., 2019). Arguably, this involves a relatively low cognitive load. Our measure of working memory manipulation requires elaborate processing of information— to reverse the order of the digits while holding these digits in the working memory. Essentially, for the digit span backward, working memory is being tested while being weighed down by an additional cognitive load. This is not something our MAP participants would have had more practice with than their HEP counterparts.

In terms of MAP-associated neuroplasticity, we observed some CT changes which are consistent with previous findings. First, there was a significant MAP-associated increase in the CT of the left ITG (at least within the first three months) and right FP. A meta-analysis (Fox et al.,

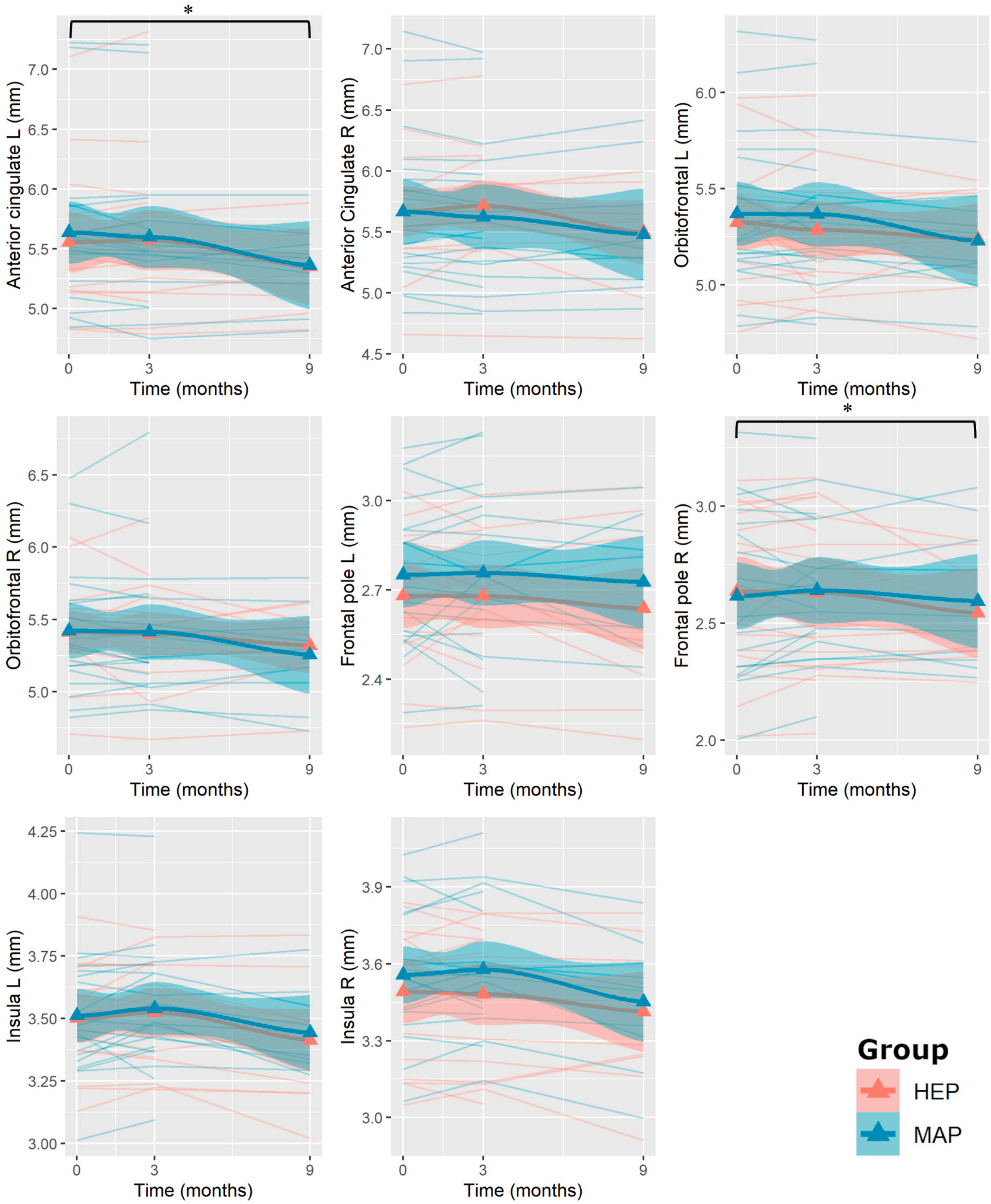

Fig. 3. Trajectories of cortical thickness values in each group across time. The thick colored lines represent the mean trajectory of each group, which are enclosed within their respective 95% confidence intervals. *p < .05.

2014) that compared between experienced meditators and meditation-naïve controls had observed similar clusters of GM volume increase in the right frontopolar cortex (including the FP) and left ITG. Relatedly, task-based functional MRI studies have shown that activations in the frontopolar cortex (Molenberghs et al., 2016) and the left ITG (Hasenkamp et al., 2012) were linked to meditation-associated meta-cognitive processes, such as meta-cognitive judgments and awareness of mind wandering. Given this, the MAP-associated CT increases in these regions could speculatively be linked to the enhanced meta-cognitive abilities typically brought about via repeated sessions of meditation. As our intervention transitioned from weekly to monthly sessions, it was observed that the increased CT in the left ITG, were no longer sustained at the ninth month. Perhaps, this suggests that the monthly meditation sessions were not adequate to maintain such gains. It is plausible that if our intervention had continued its weekly sessions, greater neuroplastic changes and perhaps cognitive gains would be observed. Indeed, a meta-analysis on mind-body exercises observed that interventions with more frequent sessions were more likely to result in greater cognitive gains than those of less frequent sessions (Chan et al., 2019).

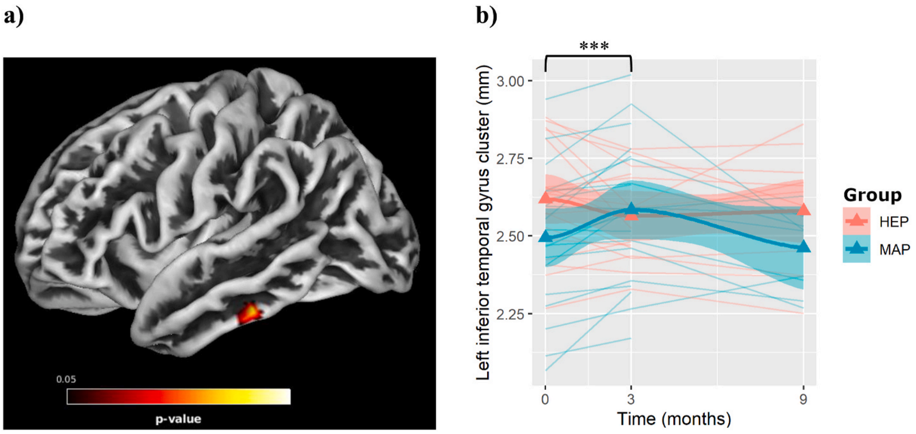

Fig. 4. a) Significant cluster (FWE-corrected $p < 0.05$) in left inferior temporal gyrus within the contrast of $\text{Time}_{\text{3-month}} > \text{Time}_{\text{baseline}}$ & MAP > HEP. b) trajectories of cortical thickness values of extracted cluster in each group across time. The thick colored lines represent the mean trajectory of each group, which are enclosed within their respective 95% confidence intervals. ***$p < .001$.

In contrast to previous cross-sectional studies that found increased ACC GM volume among experienced meditators (Fox et al., 2014), we observed a MAP-associated CT decrease in the ACC. Notwithstanding, the problems of comparing the current intervention results to cross-sectional findings, this decrease in ACC CT or volume should not always be viewed negatively, especially since the ACC is involved in several functions. One such function includes emotional processing (García-Cabezas and Barbas, 2016). In relation to this, a lesion study (Tolomeo et al., 2016) suggests that the removal of the anterior cingulate may be therapeutic for patients with intractable mood, anxiety and pain syndromes, specifically in terms of reducing negative affect. Relatedly, we speculate that the reduced ACC CT among MAP participants may reflect the neuroplastic changes corresponding to the MAP-associated attenuations in emotional reactivity to negative affect (Britton et al., 2012).

These findings present important implications in the clinical context. We have shown that a relatively low intensity (i.e., weekly or monthly sessions) non-pharmacological intervention can result in significant cognitive gains and neuroplastic changes in the context of age-related cognitive impairment. In essence, our intervention would be instrumental in delaying further cognitive decline or even enhancing one's functional status, without the side-effects of medications (Smith, 2016) or exhaustion associated with intensive cognitive training (Vranic, 2017). Additionally, the MAP-associated cognitive gains were mostly observed within the domains of executive-attention. This would suggest that such mindfulness-based interventions would be more appropriate for older adults with executive-attentional impairments, such as those with nonamnestic MCI or at risk for frontotemporal dementia, than those with amnestic MCI or at risk for Alzheimer's disease. It should also be noted that while the targeted cognitive gains are most relevant to this group of older adults, their executive functions deficits may bring about some difficulties during meditation, especially when they are required to sustain and focus their attention for a period of time.

The current study is subjected to a few limitations. First, this was an open-label study, in which both participants and the experimenters were aware of which treatment group the former was assigned to. There is a small possibility that the results may be confounded by observer-expectancy effects among experimenters and the differences in participants' treatment expectancies between both groups. Second, the attrition rate for MRI data was quite significant; by the ninth month, the number of acquired scans was less than half of that at baseline. This limits the study's ability to detect significant treatment effects on CT during the subsequent 6-month phase. Given that this attrition was largely due to various physical and psychological discomforts during the scans, future studies should attempt to alleviate some of these discomforts in order to retain as many MRI-eligible participants as possible, especially among the older adult population.

CRediT authorship contribution statement

Junhong Yu: Writing - original draft, Formal analysis, Software, Visualization. **Iris Rawtaer:** Writing - original draft. **Lei Feng:** Writing - review & editing. **Johnson Fam:** Writing - review & editing. **Alan Prem Kumar:** Formal analysis, Writing - review & editing. **Irwin Kee-Mun Cheah:** Writing - review & editing. **William G. Honer:** Writing - review & editing. **Wayne Su:** Software, Formal analysis, Writing - review & editing. **Yuan Kun Lee:** Writing - review & editing. **Ene Choo Tan:** Writing - review & editing. **Ee Heok Kua:** Writing - review & editing, Funding acquisition. **Rathi Mahendran:** Writing - review & editing, Funding acquisition, Project administration, Supervision.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.01.032.

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