Cross-sectional white matter microstructure differences in aging and mindfulness

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Abstract

The process of aging can be characterised by a decline in cognitive performance, which may be accompanied by deterioration of brain structure as well. In this study we sought to investigate to what extent mindfulness changes over the aging process, and which alterations in brain structure can be associated to aging and concomitant changes in mindfulness. We collected Mindful Attention Awareness Scale (MAAS) questionnaire data to assess mindfulness and we acquired DTI images in a group of middle-aged to elderly participants. Our results suggested that with age, mindfulness as assessed with the MAAS, increases. In terms of white-matter structure, we replicated previous findings that overall fractional anisotropy (FA) decreases with age. In an explorative analysis, we found that mindfulness predicted FA in a localized area consisting of internal and external capsule, as well as the corona radiata. We speculated that mindfulness might deter age-associated neurocognitive decline, perhaps by preventing age-associated microlesions specifically in cortico-subcortical white matter tracts. This possibility invites future interventions or longitudinal studies to confirm this hypothesis.

Keywords: Age; DTI; FA; Mindfulness

Introduction

Healthy aging has become an important topic of research, as increasingly effective healthcare is keeping our elders alive longer. Life expectancy has been increasing since the industrial revolution and is approaching an average of 70 years worldwide (Roser, 2017a). Birthrates have gone down in many countries, especially in those with low child mortality rates (Roser, 2017b). In the upcoming years, wealthy countries will see larger cohorts of elderly as compared to younger individuals. This shift in the population's age distribution increases the importance of neuropsychological research aimed at finding efficient ways of maintaining mental health in aging.

Cognitive decline is generally accepted as a "normal" part of aging. Yet, not all cognitive processes will decline with age. So far, research has shown that some cognitive processes (e.g., vocabulary, world knowledge) are less impaired while other cognitive processes such as speed of processing, working memory, and reasoning show large decrements with increasing age (Park & Bischof, 2013). In particular, many studies have provided evidence showing that older adults have deteriorated cognitive control functions, such as less working memory capacity (Grady & Craik, 2000; Salthouse, 1994; West, 1996), a deficit in inhibitory processing (Hasher & Zacks, 1988; Kramer, Humphreys, Larish, & Logan, 1994), and a lack of cognitive flexibility (Kramer, Hahn, & Gopher, 1999; Mayr, 2001). One possible fundamental deficit that triggers these cognitive problems with increasing age is a general decrease in the *control* over task-relevant mental processes. That is, it is increasingly more difficult for older adults to apply new rules, to coordinate multiple rules, and to maintain relevant information in the context of interfering one.

More practically, age-related declines in cognitive functions have been shown to be associated with severe deficits on the elders' everyday life activities. For example,

some researchers have found performance on cognitive assessments to be associated with instrumental activities of daily living (IADL; e.g., paying bills, shopping for groceries; see Cahn-Weiner, Boyle, & Malloy, 2002; Grisgby, Kaye, Baxter, Shetterly, & Hamman, 1998). There are findings showing that updating in working memory and task-switching had the strongest relationships with IADL (three domains: home management, financial management, and health and safety). There are also findings showing that cognitive function influenced self-care capacity. For example, learning proper inhaler-use technique has been found to be associated with higher scores on the Executive Interview among older adults (Allen, Jain, Ragab, & Malik, 2003). In addition, older adults who exhibited poor performance on tests measuring cognitive flexibility have been found to have increased difficulty in everyday problem solving.

Cognitive function and flexibility have been found to be intimately linked with mindfulness (Moore, Gruber, Derose, & Malinowski, 2009; Baer, 2003). It is important to investigate whether mindfulness plays a role in the aging process. Accumulating evidence suggests that mindfulness-based interventions (MBI; Cullen, 2011; Eberth & Sedlmeier, 2011, Prakash et al., 2014) may provide a way to deter the detrimental effects of aging, by promoting cognitive and emotional health (Moore et al., 2012; Zeidan et al., 2010; Luders & Cherbuin, 2016). Mindfulness based interventions may work because they provide a more holistic attentional training, in the sense that they allow training of general attentional mechanisms, the improvement of which benefit many cognitive tasks. However, neurocognitive research on mindfulness is scarce, and the effect of mindfulness on brain structure has not been elucidated yet. Studies report neural benefits of mindfulness such as increases of overall brain FA (Luders et al., 2011) and altered concentrations of important brain

metabolites (Fayed et al., 2013; see Fox et al., 2014 and 2016 for reviews on the neurocognitive underpinnings of mindfulness meditation). These findings are interesting, yet seem too few in number to draw general conclusions from.

Additionally, it remains unclear to what extent individual differences in mindfulness may interact with the aging process, and whether these interactions are reflected in individual differences in brain structure and plasticity. A more recent study by Goh et al. (2012) based on the database of Baltimore Longitudinal Study of Aging (BLSA) has shown heterogeneous performance trajectories across cognitive domains and across individuals (Goh, An, & Resnick, 2012). Differences in the cognitive trajectories of healthy older adults (Yaffe et al., 2009) suggest that cognitive decline may not be a necessary consequence of ageing, but may result from a range of risk factors that become more prevalent with increasing age. Understanding the mechanisms that contribute to different trajectories of cognitive decline in clinically intact older adults is a significant target for the prevention or reduction in progression of cognitive decline and dementia in old age.

To address the above two research questions, i.e., ‘how mindfulness may have the effect on brain structure’ and ‘to what extent individual differences in mindfulness may interact with age’, we set out to investigate firstly whether mindfulness shows an association with age, which could suggest age-related differences in mindfulness state. Secondly we asked whether brain structural differences can inform us about age and mindfulness. In order to answer these questions, in a group of elderly we acquired DTI images in combination with a questionnaire survey containing the Mindful Attention Awareness Scale (MAAS; MacKillop & Anderson, 2007).

Methods

Participants

Participants recruited in the present study were part of a larger lifespan data set collected at National Cheng Kung University. The original cohort of older adults was 60 years old, recruited to participate in this study by advertisement. All participants were right-handed (Edinburgh Handedness Inventory; Oldfield, 1971), in good general health, without major neurological and psychological disorders, and had normal or corrected-to-normal vision. Demographic information about these 97 participants is described in Table 1. All subjects provided written informed consent, and the study protocol was approved by the Research Ethics Committee of National Cheng Kung University. All subjects were paid 1,500 NTD (around $50 USD) after completion of the experiment.

Table 1. Demographics information

	Mean	Range	SE
Age	57.26	40-77	0.95
Education	13.72	4-18	0.30
MoCA	26.80	22-30	0.19
BDI-II	5.12	0-13	0.42
PSQI	6.16	1-14	0.35
MAAS	61.48	41-90	1.15

Note. SE: standard error; MoCA: Montreal Cognitive Assessment; BDI-II: Beck Depression Inventory II; PSQI: Pittsburgh Sleep Quality Index; MAAS: Mindful Attention Awareness Scale.

Questionnaires

Data presented in this paper come from a subset of the battery of demographic, neuropsychological and cognitive tasks completed in the larger lifespan study as a whole. The current investigation concerns itself with the following tests: (1) The Montreal Cognitive Assessment (MoCA) was used to screen participants for probable dementia (Nasreddine et al., 2005). (2) The Beck Depression Inventory (BDI-II) was used to screen depression (Beck, Steer, & Brown, 1996). (3) A traditional Chinese for

Taiwan version of the Pittsburgh Sleep Quality Index-PSQI was used to measure the quality and patterns of sleep (Buysse et al., 1989). (4) The 15-item Mindful Attention Awareness Scale (MAAS) was used to measure trait mindfulness (Black et al., 2012). All questionnaires took between 5 and 10 minutes to complete.

Imaging Protocols

MRI images were acquired using a GE MR750 3T scanner (GE Healthcare, Waukesha, WI, USA) in the Mind Research Imaging (MRI) center of National Cheng Kung University. High resolution structural images were acquired using fast-SPGR, consisting 166 axial slices (TR/TE/flip angle, 7.6 ms/3.3 ms/12◦; field of view (FOV), 22.4 × 22.4 cm2; matrices, 224 × 224; slice thickness, 1 mm), and the entire process lasted for 218 s. Diffusion weighted imaging (DWI) were obtained with a spin-echo-echo planar sequence (TR/TE = 5500 ms/minimum, 50 directions with b= 1000 s/mm2, 100 x 100 matrices, slice thickness = 2.5 mm, voxel size = 2.5 x 2.5 x 2.5 mm, number of slices = 50, FOV = 25 cm, NEX = 3). 6 non-diffusion-weighted (b = 0 s/mm^2) volumes were acquired, 3 of which with reversed phase encoding so as to allow correction for susceptibility induced distortions.

DWI processing

All DWI data processing and analyses were carried out using FMRIB's Software Library (FSL, version 5.0.9; www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Diffusion weighted images were first converted from DICOM to NIFTI format using the MRIcron's dcm2nii tool (https://www.nitrc.org/projects/mricron/). TOPUP (Andersson et al., 2003; Smith et al., 2004) and EDDY (Andersson & Sotiropoulos, 2016) were used to clean the DWI images of artefacts caused by susceptibility induced distortions, eddy currents, and head motion. A single image without diffusion weighting (b0; b value = 0 s/mm2) was extracted from the concatenated data, and

nonbrain tissue was removed using FMRIB's brain extraction tool (Smith, 2002) to create a brain mask that was used in subsequent analyses. DTIFIT (Behrens et al., 2003) was applied to fit a tensor model at each voxel of the data to derive fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) measures for further analyses.

In order to perform tract-based investigations into DTI measures we performed tract-based spatial statistics (TBSS; Smith et al., 2006) in FSL. FA images were slightly eroded and end slices were zeroed in order to remove likely outliers from the diffusion tensor fitting. The images were then nonlinearly aligned to each other and the most representative image was then identified. This target image was subsequently affine transformed to 1mm MNI space. FA images were transformed to 1mm MNI space using combination of the nonlinear and affine registration. A skeletonization procedure was then performed on the group-mean FA image, the result of which was thresholded at FA > 0.2 to identify areas most likely to belong to white matter tracts of nontrivial size.

Statistical analyses

Linear regressions were performed in R (version 3.0.2; R Foundation for Statistical Computing, http://www.R-project.org) to test for (1) a linear association between participant's age and their self-reported MAAS mindfulness score, controlling for gender and MoCA, BDI, and PSQI scores as regressors of no interest, and (2) a linear association between DTI measures (i.e., FA, MD, RD, AD) and age, controlling for gender, and MoCA, BDI, PSQI, and MAAS scores (1 regression per measure). In addition, we performed a mediation analysis predicting age based on FA, using MAAS scores as a mediator. For the Bayesian version of these tests we used the BayesFactor (http://bayesfactorpcl.r-forge.r-project.org/) and BayesMed

(https://CRAN.R-project.org/package=BayesMed; Nuijten et al., 2015) toolboxes. For the voxel-wise univariate regressions we used FSL's randomise function on a model mimicking our whole-brain average regressions, testing for a linear association between FA and MAAS scores, controlling for age, gender, and MoCA, BDI, and PSQI scores.

For both the behavioral and DTI results we report classical frequentist p-values, as well as Bayes factors, which provide a more conservative evaluation of the correlations. For ease of reading, we provide both BF_{10} (Bayes factor for the presence of a correlation) and BF_{01} (Bayes factor for the absence of a correlation). These are inversely related (i.e., $BF_{10} = 1/BF_{01}$ and $BF_{01} = 1/BF_{10}$). Bayes factors may be interpreted as proportional evidence for the presence or absence of an effect. For instance BF_{10} of 5 may be interpreted as the data being 5 times more likely to occur under the alternative hypothesis then under the null-hypothesis. In addition, we can interpret the Bayes factor categorically based on a grouping proposed by Jeffreys (1961). Table 2 shows this evidence categorization for the BF_{01}, edited by and taken from Wetzels and Wagenmakers (2012; Table 1, p. 1060). For a detailed explanation of the Bayesian statistics and the Bayes factor, see Ly et al., 2016.

Table 2. Suggested categories for interpreting Bayes factors based on Jeffreys (1961).

Bayes factor BF_{01}			Interpretation
	>	100	Extreme evidence for H_0
30	-	100	Very Strong evidence for H_0
10	-	30	Strong evidence for H_0

Bayes factor BF_{01}			Interpretation
3	-	10	Moderate evidence for H_0
1	-	3	Anecdotal evidence for H_0
	1		No evidence
1/3	-	1	Anecdotal evidence for H_1
1/10	-	1/3	Moderate evidence for H_1
1/30	-	1/10	Strong evidence for H_1
1/100	-	1/30	Very Strong evidence for H_1
	<	1/100	Extreme evidence for H_1

Results

Age and MAAS

We performed a linear regression predicting age based on MAAS scores. Gender and MoCA, BDI, and PSQI scores were added to the GLM as regressors of no interest. A classical linear regression showed a significant association of MAAS scores (t = 3.267, p = 0.00154; Fig. 1) with age, suggesting that older individuals have higher mindfulness scores than younger individuals (note our sample's age range: 40 - 77). In addition, a Bayesian linear regression showed strong evidence of a positive association between age and MAAS (BF_{10} = 206.9).

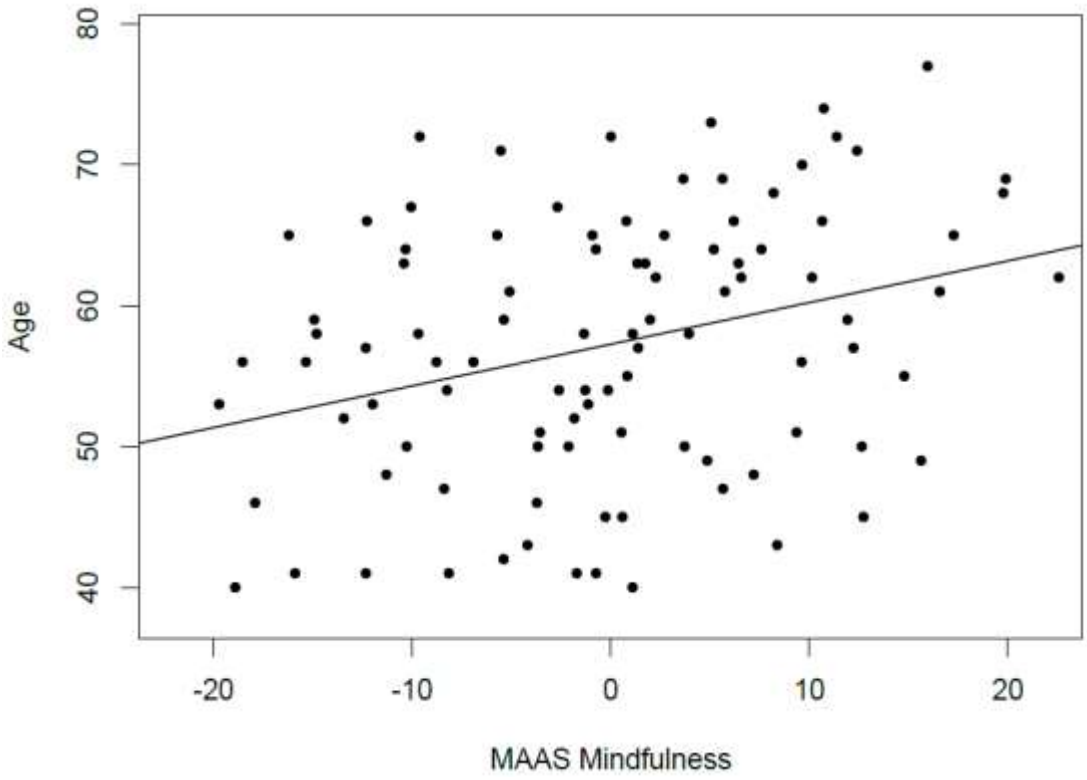

Fig. 1. Positive correlation beween age and mindfulness assessed by Mindful Attention Awareness Scale (MAAS). Scatterplot with regression line.

DTI and Age

We performed a linear regression predicting whole brain average FA based on age while regressing out variance attributed to gender, and scores on MAAS, MoCA, BDI, and PSQI. We observed a negative correlation between FA and age (t = -5.497, p = 0.000000357, BF_{10} = 21379, Table 3 & Fig. 2), suggesting that in older individuals the diffusion tensor is less fractionally anisotropic than in relatively younger individuals. Increases in FA may arise from both a relative decrease in radial diffusivity (RD), as well as from a relative increase in axial diffusivity (AD). In addition, mean diffusivity (MD) provides information about the overall omnidirectional diffusion. To elucidate the precise nature of the tensor transformation leading to our observed FA-age relation, we also extracted whole-brain skeleton-

averaged RD, AD, and MD, and regressed these against subject's age (again controlling for gender, MAAS, MoCA, BDI, and PSQI). Results can be seen in table 3. We observed a positive relation between RD and age (t = 5.033, p = 0.00000246, BF_{10} = 9540; Fig. 3), and non-significant positive relation between AD and age (t = 1.895, p = 0.0613, BF_{10} = 1.546). For the purpose of understanding the nature of the tensor transformation underlying our observed FA-age effect, it is sufficient to attend to the direction of the correlation, which is positive, indicating an increase in diffusion along the principle diffusion direction (i.e., AD). For the negative FA-age correlation to emerge, the RD has to sufficiently increase as well, which indeed seems to be the case. In addition, we observe a positive correlation between MD and age (t = 4.286, p = 0.0000455, BF_{10} = 754.7; Fig. 4), in accordance with the increase in both AD and RD. As such, we may expect that with age there is a general increase of omnidirectional diffusion, which favours radial over axial diffusivity, leading to a decrease in FA. This cross-sectional effect serves as a hypothesis for longitudinal follow-up phases of this study.

Table 3. Correlation between FA/MD/RD/AD and Age

	t	*p*	BF_{10}	BF_{01}
FA	-5.497	0.000000357	21379	0.00004677
MD	4.286	0.0000455	754.7	0.001325
RD	5.033	0.00000246	9540	0.0001047
AD	1.895	0.0613	1.54641	0.6467

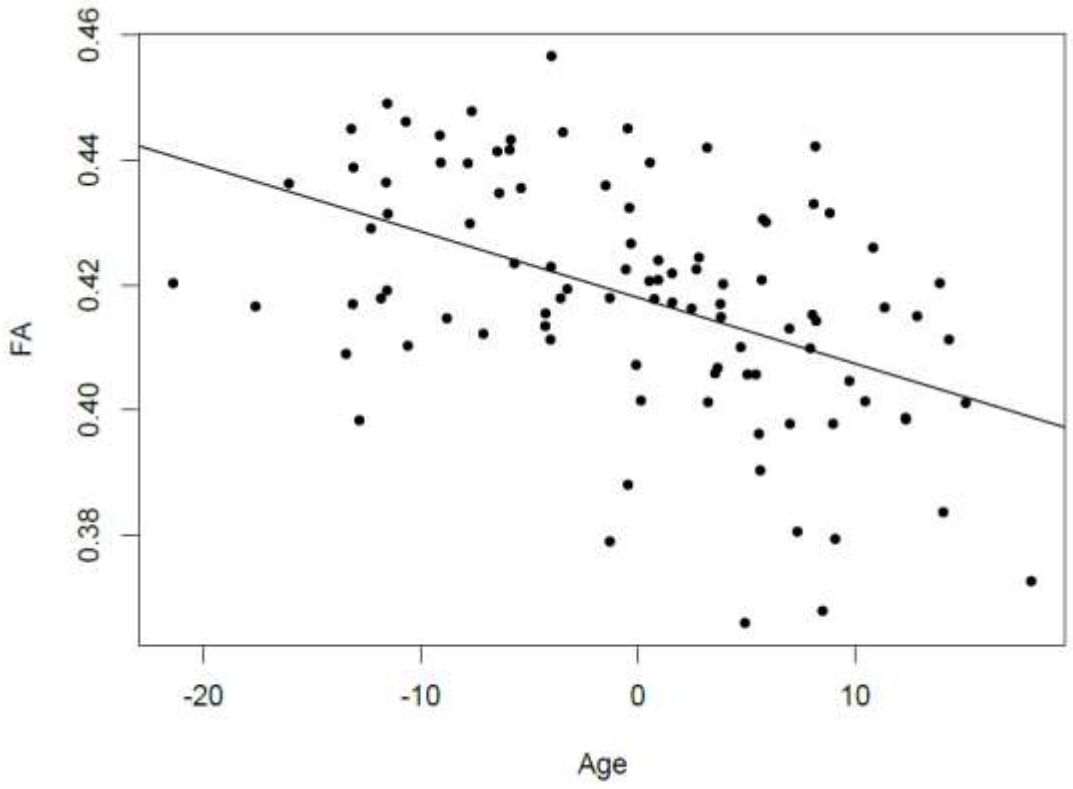

Fig. 2. Negative correlation between FA and age. Scatterplot with regression line.

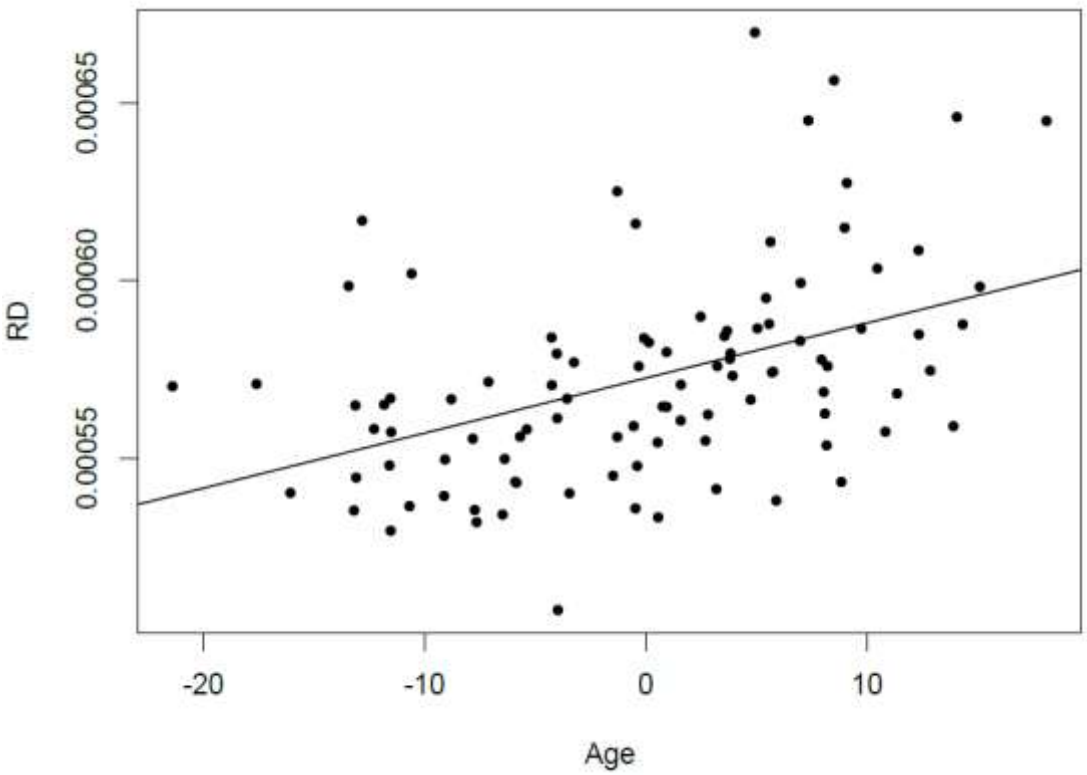

Fig. 3. Positive correlation between RD and age. Scatterplot with regression line.

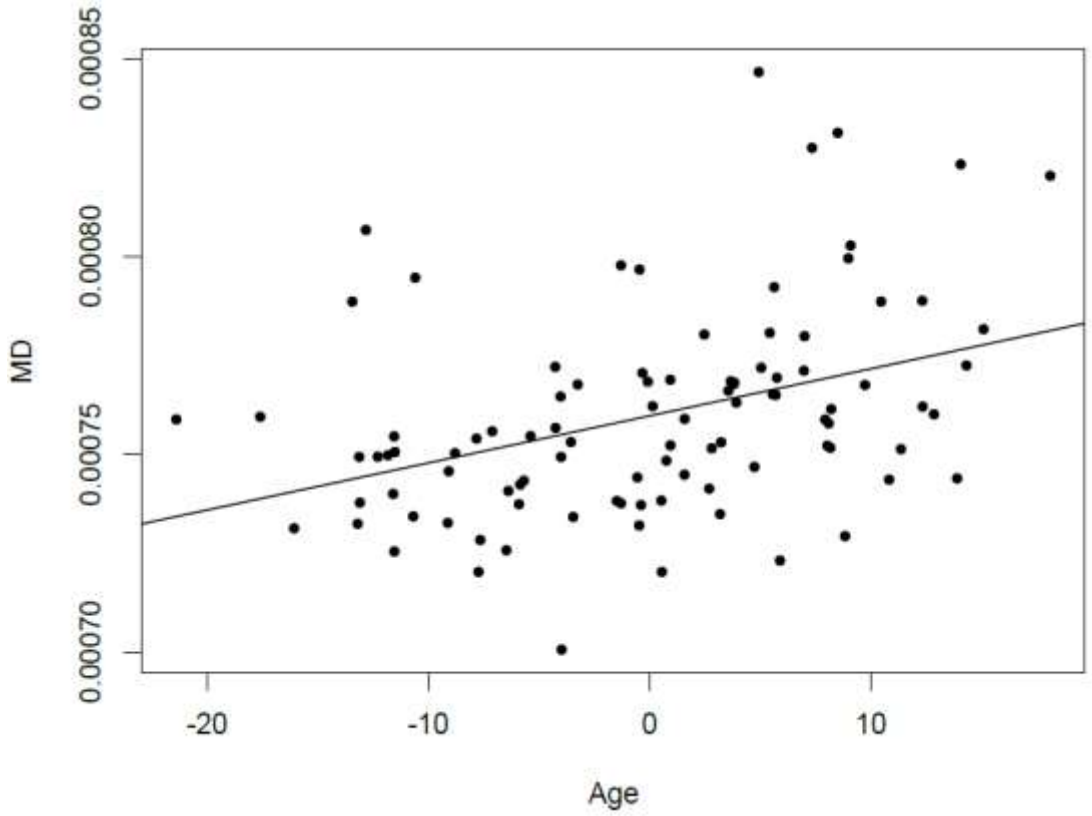

Fig. 4. Positive correlation between MD and age. Scatterplot with regression line.

DTI and MAAS

In addition to cross-sectional age differences, we were interested in cross-sectional differences in DTI measures relating to MAAS scores. We performed a linear regression between DTI measures and MAAS, while regressing out age, gender, and scores on MoCA, BDI, and PSQI. In addition, we performed a more explorative mass univariate regression within the whole-brain skeleton in which we attempted to pinpoint spatially located associations between MAAS and white matter microstructure.

We found no significant relation between MAAS and FA ($t = 1.095$, $p = 0.2764$, $BF_{10} = 0.2977$). Inverting the Bayes factor here provides with substantial evidence in favor of the null-hypothesis (the absence of a relation), $BF_{01} = 3.576$. We

subsequently investigated the remaining DTI measures MD, RD, and AD, which were also found not to be associated with MAAS scores (all $BF_{01} > 3$, Table 4).

Table 4. Correlation between FA/MD/RD/AD and MAAS

	t	*p*	BF_{10}	BF_{01}
FA	1.095	0.2764	0.2977	3.576
MD	0.074	0.9415	0.3126	3.199
RD	-0.311	0.7563	0.3281	3.048
AD	1.026	0.3075	0.2530	3.952

We performed an additional, more explorative mass-univariate regression analysis within the whole-brain white matter skeleton in order to pinpoint spatially localized relations between MAAS and tensor-derived measures. We found a positive relation between FA and MAAS in the left hemisphere, specifically in the internal and external capsule, extending widely from the anterior to the posterior parts of both these white-matter tracts, and extending dorsally into the corona radiata ($t = 5.482$, $p < 0.05$ corrected for multiple comparisons; Fig. 5). As mentioned previously, differences in FA can be driven by differences in RD as well as AD, so we extracted the mask-average AD and RD from the voxels showing a positive relation between FA and MAAS. We found a positive relation between AD and MAAS scores ($t = 3.479$, $p = 0.000777$, $BF_{10} = 8.90$), and a negative relation between RD and MAAS scores ($t = -3.687$, $p = 0.000387$, $BF_{10} = 3.02$). As such, it seems that in individuals with a higher self-report score on the MAAS mindfulness scale, the diffusion tensor displays a relatively decreased RD, and a relatively increased AD, as compared to

low-mindfulness individuals, leading to an overall increase of FA in mindful individuals, in the internal and external capsule, extending dorsally into the corona radiata.

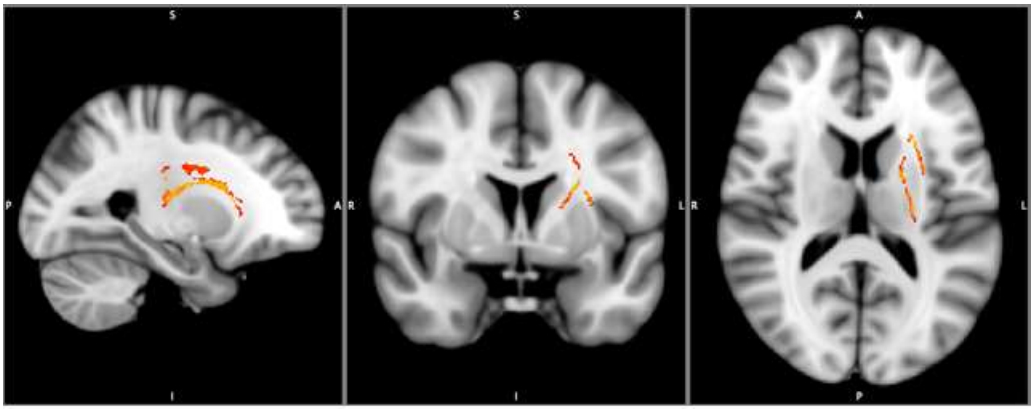

Fig. 5. FA-MAAS correlation at coordinates: 115, 128, 86.

In light of this finding we were additionally interested in whether MAAS may serve as a mediator between age and FA within the spatially localized area which showed significant MAAS-FA associations. A mediation analysis showed that MAAS was indeed mediating the association between FA and age within this area (BF_{10} = 45.39). We interpret this finding to suggest that as individuals age, FA in this region is preserved, especially for individuals who self-report to be more mindful.

Discussion

In this study we sought to investigate the relation between characteristics of white matter microstructure, age, and MAAS. To this end we acquired diffusion weighted imaging data in combination with a set of questionnaires (MAAS, MoCA, BDI, PSQI) on a group of elderly participants. We found that age was positively associated with MAAS suggesting that older individuals tend to have higher mindfulness scores. Raes et al. (2013) have also found a similar age-MAAS effect, as well as Mahoney et al. (2015), although they use a younger age ranges and nonlinear aging effects have

been observed. From our data it is unclear why or how mindfulness and attentional capabilities fluctuate over the lifespan.

In terms of DTI metrics and age our results suggested that in older participants there is a general increase of omnidirectional diffusion, which favours radial over axial diffusivity, leading to a decrease in FA. This is consistent with previous findings which also showed a general decline in FA with age (Salat et al., 2005; Sullivan et al., 2010; Vernooij et al., 2008; Jolly et al., 2016).

Our explorative voxelwise investigation into DTI metrics and MAAS found a localized positive association between FA and MAAS in the left hemisphere corona radiata and the internal and external capsule. It is interesting to note that Tang et al (2010, 2012) found that by training participants using a form of mindfulness meditation, integrative body-mind training (IBMT), FA increased in the corona radiata, which accords with the current finding of a positive correlation between FA and MAAS in the left hemisphere cornona radiata. However, research into structure-function associations in mindfulness have been scarce, and the literature is not yet unified. For example, Luders et al. (2011) found larger FA in different brain structures to be associated with mindfulness training, including a fiber tract constituting the temporal component of the superior longitudinal fasciculus (tSLF) and a fiber tract linked to the hippocampus such as uncinated fasciculus (UNC). On the other hand, Tang et al. (2010) and Holzel et al. (2011) observed larger FA in an entire fiber tract connecting frontal and tempro-parietal regions, such as SLF, and in a fiber bundle linked to the hippocampus such as cingulate cortex hippocampus (CgH), to be associated with active mediation practices. Furthermore, in addition to the aforementioned DTI-based studies, Fox et al. (2014) reviewed and used activation likelihood estimation to meta-analyze on the brain structures underpinnings of

mindfulness, in which they observed larger voxel based morphometry in intra- and interhemispheric communication (e.g., SLF; corpus callosum) to be associated with meditation. Given these various findings regarding which fiber tracts that are related to mindfulness experience, futher studies are needed to clarify the issue. In particular, how to determine the exact extent/intensity of the individual meditation/mindfulness training is essential to yield a fair across-study comparison.

Turning back to the current finding of a positive correlation between FA and MAAS in the left hemisphere cornona radiata, what could be the role of the internal and external capsule and the connecitons with the corona radiata in aging and mindfulness? Some researchers have hypothesized some psychological mechanisms that are associated with neural mechanisms of mindfulness meditation respectively. For example, Holzel and colleagues (2011) suggested that there are consisting of at least four possible psychological components: (1) attention regulation, (2) body awareness, (3) emotion regulation: (a) reappraisal and (b) exposure, extinction, and reconsolidation, and (4) change in perspective on the self (Holzel et al., 2011). These four psychological components have been shown to be associated with neural activation in some specific brain areas respectively, including (1) anterior cingulate cortex (ACC), (2) insula, temporo-parietal junction, (3a) dorsal prefrontal cortex (dPFC), (3b) ventro-medial PFC, hippocampus, and amygdala, and (4) medial PFC, posterior cingulate cortex, insula, and temporo-parietal junction (see Holzel et al., 2011, Table 2). Based on these neural evidence in association with different facets of mindfulness meditation (intention, attention, attitude, body awareness, reappraisal, and changes in perspectives on self), Grecucci and colleagues (2015) suggest that there are top-down and bottom-up neural circuits in the processes of mindful emotion regulation. These circuits include top-down control regions such as the PFC and the

ACC and bottom-up emotional regions such as the insula (I) and the amygdala (A). Grecucci et al. (2015) further suggested that these two neural circuits (PFC-ACC & A-I) may interact with each other via connective neural structures such as the corona radiata. Therefore, the current DTI finding of the tract of corona radiata positively correlated with MAAS appears to be reconciled with Grecucci et al.'s (2015) postulation, in which the increased FA in corona radiata may facilitate the connection between the two neural circuits (PFC-ACC & A-I) hence resulting in highly associated with MAAS.

It is worth noting that the FA-MAAS association is characterised by a thinning and elongation of the diffusion tensor, this is both due to AD increasing with respect to MAAS, as well as RD decreasing. As such, it seems the white-matter in this area is more streamlined for individuals who self-report to be more mindful. The tensor model used here cannot directly inform us about the biological causes of these effects (Jones et al,. 2013), although we could speculate that an overall loss of FA due to white matter lesions occurs with age (Vernooij et al., 2008), and that mindfulness in life may prevent some of these lesions. This speculation can be supported by the current mediation analysis showing that MAAS was indeed mediating the association between FA and age within the internal and external capsule, as well as the corona radiata. Future studies could test this hypothesis by employing mindfulness-based interventions longitudinally, since the cross-sectional nature of this study precludes a direct observation of age-related change.

Conclusion

Surprisingly, the current results showed that with increasing age, an individual's mindfulness tends to increase, but on the contrary, whole-brain overall FA decreases due to increasing omnidirectional diffusion. Between individuals, FA in a localized

area consisting of internal and external capsule as well as the corona radiata, showed an increase with mindfulness. Interestingly, we subsequently found that mindfulness mediates an FA-age effect in this localized area. Therefore, we speculate that mindfulness may deter age-associated neurocognitive decline, perhaps by preventing age-associated microlesions specifically in cortico-subcortical white matter tracts. This possibility invites future interventions or longitudinal studies to confirm it.

Disclosure statement

Conflict of Interest: The authors have no actual or potential conflicts of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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