Mechanisms of white matter changes induced by meditation

Yi-Yuan Tang[a,b,c,1], Qilin Lu[b], Ming Fan[d], Yihong Yang[e], and Michael I. Posner[c,1]

[a]Department of Psychology, Texas Tech Neuroimaging Institute, Texas Tech University, Lubbock, TX 79409; [b]Institute of Neuroinformatics and Laboratory for Body and Mind, Dalian University of Technology, Dalian 116024, China; [c]Department of Psychology, University of Oregon, Eugene, OR 97403; [d]Institute of Basic Medical Sciences, Beijing 100850, China; and [e]Neuroimaging Research Branch, National Institute on Drug Abuse-Intramural Research Program, Baltimore, MD 21224

Using diffusion tensor imaging, several recent studies have shown that training results in changes in white matter efficiency as measured by fractional anisotropy (FA). In our work, we found that a form of mindfulness meditation, integrative body–mind training (IBMT), improved FA in areas surrounding the anterior cingulate cortex after 4-wk training more than controls given relaxation training. Reductions in radial diffusivity (RD) have been interpreted as improved myelin but reductions in axial diffusivity (AD) involve other mechanisms, such as axonal density. We now report that after 4-wk training with IBMT, both RD and AD decrease accompanied by increased FA, indicating improved efficiency of white matter involves increased myelin as well as other axonal changes. However, 2-wk IBMT reduced AD, but not RD or FA, and improved moods. Our results demonstrate the time-course of white matter neuroplasticity in short-term meditation. This dynamic pattern of white matter change involving the anterior cingulate cortex, a part of the brain network related to self-regulation, could provide a means for intervention to improve or prevent mental disorders.

attention network test | anterior corona radiata | profile of mood states

Diffusion tensor imaging (DTI) is a noninvasive MRI-based technique that can delineate white matter fibers in vivo. DTI is capable of measuring white matter's structural plasticity. Studies indicate that training or learning alters brain white matter (1–5). Fractional anisotropy (FA) is an important index for measuring the integrity of white matter fibers. In general, a higher FA value has been related to improved performance, and reduced FA has been found in normal aging and in neurological or psychiatric disorders (1, 6–8).

FA alterations originate from several factors, such as changes in myelination, axon density, axonal membrane integrity, axon diameter, and intravoxel coherence of fiber orientation and others changes (1, 9). To understand the mechanisms of FA change, several DTI studies have examined axial diffusivity (AD) and radial diffusivity (RD), the most important indices associated with FA (6–8). Usually, alterations in AD are associated with axon morphological changes, such as changes in axonal density or caliber (10, 11). In contrast to AD, which signifies axonal morphology, RD implicates the character of the myelin. Decrease in RD implies increased myelination, and increase represents demyelination (2, 3, 8). This evidence in human neuroimaging studies is consistent with animal studies examining axons and myelination histologically and comparing them directly with DTI results (12, 13).

To examine RD and AD it is best to have a significant change in FA (14). Thus, in our study we investigated AD and RD alteration patterns only where integrity of white matter fibers are enhanced (identified by FA increase). Numerous studies have used AD and RD changes in the location where FA changes are found to determine whether the FA changes are a result of axonic morphology or myelin (1–3, 6, 8, 14, 15).

Studies of normal aging and Alzheimer's disease have found FA decreases, and reported different patterns of AD and RD alteration. Depending upon the brain region examined, these studies found either only RD increase, or both RD and AD increase, or RD increase and AD decrease (6–8). These results showed considerable diversity in the way in which brain regions respond to aging or neurodegenerative diseases. In contrast to aging, training in reading, use of the abacus, and working memory have resulted in FA increase by decreasing RD without changing AD. This pattern supports the notion that myelination is the predominant process of the increased FA following training in specific tasks (2–4). Keller and Just (3) proposed that skill learning would increase neural firing and thus increase myelination (decrease in RD and increase in FA). The increased myelination would enhance communication among cortical areas, resulting in better performance.

Our previous study showed that 4 wk of integrative body–mind training (IBMT) (11 h in total) enhanced FA in several brain areas involved in communication to and from the anterior cingulate cortex (ACC), including the corpus callosum and anterior and superior corona radiata (5). However, whether the FA increase is a result of changes in AD or RD in our study is unknown. We proposed that IBMT improves attention and self-regulation via a change in brain state (16, 17) rather than directly training an attentional network. Thus, it is possible that IBMT may not work in a way exactly similar to general skill training. In this article, we first investigate mechanisms of meditation-induced white matter changes by examining AD and RD alterations in brain areas where we reported FA changes after 4 wk of IBMT. We then examined white matter changes after 2 or 4 wk of training to determine which index of white matter change is more sensitive to the different amounts of training.

Results

Our previously reported study (5) randomized 45 University of Oregon undergraduates to 4-wk IBMT or relaxation training (RT) and used MRI to assess white matter integrity before and after training. After 4-wk training, the IBMT group increased FA in several brain regions but the RT group did not (5). We then analyzed changes of AD and RD in those areas where the FA value was increased by 4-wk IBMT. We found two patterns of FA increase were statistically significant after correction for multiple comparisons (all $P_{FWE} < 0.05$). The first pattern was FA increase involving simultaneous decreases of AD and RD. The second pattern was FA increase accompanied by only a decrease in RD. The first pattern (labeled as FA↑AD↓RD↓, pattern 1) occurred in all six brain regions in which FA was found to increase. The second pattern (labeled as FA↑RD↓, pattern 2) occurred in parts of four of the brain regions in which FA increased. Results are

NEUROSCIENCE

Table 1. Different patterns of FA increase after 4-wk IBMT

Brain regions	FA↑with AD↓RD↓ (Pattern 1) (mm³)	FA↑ with RD↓ (Pattern 2) (mm³)
Genu of corpus callosum	102	
Body of corpus callosum	407	132
Anterior corona radiata L	242	260
Superior corona radiata R	52	
Superior corona radiata L	63	96
Superior longitudinal fasciculus L	25	23

summarized in Table1. For example, the left anterior corona radiata showed patterns 1 and 2; the genu of corpus callosum only showed pattern 1. Generally, each area has one subarea with pattern 1 and a nonoverlapping subarea with pattern 2. No areas showed greater change with 4 wk of RT than with IBMT (all *P* > 0.05). All six regions had voxels showing pattern 1, but four of these areas also had voxels showing pattern 2. It should be noted that when two patterns were found they were in contiguous areas within the general brain region. Except at the boundary, no voxel showed pattern 1 when an adjacent voxel showed pattern 2.

In Fig. 1, we demonstrate four regions on the Johns Hopkins University Atlas (18) showing FA increase, and AD and RD decrease at the sagittal section after 4-wk IBMT. These regions were: body of corpus callosum, genu of corpus callosum, anterior corona radiata, and superior corona radiata.

To examine how these changes in white matter arose, we compared FA, RD, and AD after 2-wk training. In study 2, we randomly assigned 68 Chinese undergraduates to an IBMT group or to an RT group (34 each group). Before training, no significant difference in FA, AD, or RD was detected between the two groups. After 2-wk IBMT (5 h total), we found a significant decrease of AD in the corpus callosum, corona radiata, superior longitudinal fasciculus, posterior thalamic radiation, and sagittal stratum using a whole-brain analysis with a correction for multiple comparisons (all $P_{\mathrm{FWE}} < 0.05$) (Fig. 2), but changes in FA and RD did not reach significance. Meanwhile, the same amount of RT did not show any significant change for any white matter index of FA, AD, or RD.

Our previous studies indicated 1-wk IBMT improved attention and self-regulation using an attentional network test and a profile of mood states (POMS) (19). We found significant behavioral changes following 2-wk IBMT in the POMS, an index of mood. Before training, there was no significant difference between the

IBMT and RT groups ($P > 0.05$). After training, *t* tests showed significant reductions in anger-hostility (A), confusion-bewilderment (C), depression-dejection (D), fatigue-inertia (F), and total mood disturbance (TMD) in POMS (all $P < 0.05$) in the IBMT group (but not the relaxation group). After training, correlations between TMD change and AD decrease at the left posterior corona radiata ($r = 0.409$) and TMD change and AD decrease at the left sagittal stratum ($r = 0.447$) were significant (all $P < 0.05$), indicating the training-induced change in mood was correlated with the brain changes in these areas (Figs. 3 and 4).

Discussion

Our studies have shown that short-term meditation training increases the ability to resolve conflict in a cognitive task, altered neural activity in the ACC, and improved connectivity of the ACC to other brain regions (5, 16, 17, 19, 20). The ACC has been associated with the ability to resolve conflict and to exercise control of cognition and emotion (21). One study found a correlation between the ability to resolve conflict and FA in the anterior corona radiata, a major pathway connecting the ACC to other brain areas (22). Thus, the improved self-regulation following IBMT may be mediated by the increase of communication efficiency between the ACC and other brain areas (5, 16).

In the present study we examined the pattern of AD and RD changes as a result of IBMT in brain areas where FA value increased. The pattern of FA increase with only RD decrease has been found in reading, working memory, and abacus training studies (2–4), but 11 h of IBMT improves FA in a different way. With IBMT we typically found two patterns of change: in pattern 1 both AD and RD decrease, and in pattern 2 only RD decreases. AD decrease has also been found in early brain development and is interpreted as reduced interaxonal space caused by increasing axonal density or caliber (10, 11). The present results imply that enhanced integrity of white matter fibers by IBMT may be caused by increased numbers of brain fibers or increased axonal caliber. Decrease of RD value was another important character of effects of 11 h of IBMT. Several studies have indicated that RD decrease is related to increased myelination (2–4, 23, 24). Myelination has been found in animal and human studies to be modifiable by experience, and affects information processing by regulating the velocity and synchrony of impulse conduction between distant cortical regions (23, 24). Increased myelination could occur because of increased neural firing in brain areas active during training (2–4). Changes in the ACC activation and its connectivity have been found in both meditation (5, 16, 25) and other forms of training (26, 27). However, IBMT differs from other forms of cognitive training in showing significant decreases in both AD and RD, suggesting that IBMT may have a different mechanism from skill training or learning with specific tasks for which only RD changes have been reported (16, 17). Other plausible explanations of differences might be because of different methods of analysis or power used so that further, more direct comparisons are needed to clarify this.

Generally, FA value has shown less sensitivity than its components, with AD reflecting axonal morphological changes and RD indexing myelination (28). We found that after 2 wk of
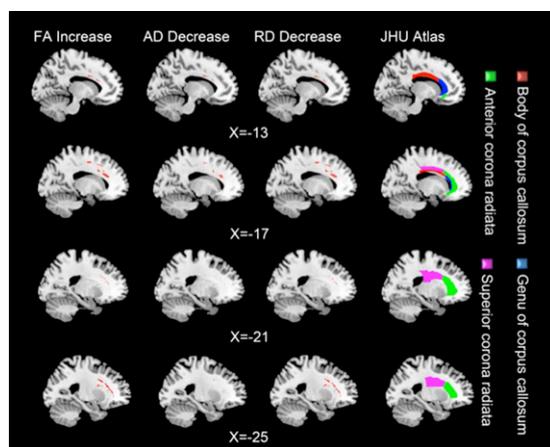

Fig. 1. FA increase and AD and RD decrease in different brain regions after 4-wk IBMT. Statistical images are shown on the Johns Hopkins University Atlas (18) at $P_{\mathrm{FWE}} < 0.05$ corrected for multiple comparisons at sagittal section $x = -13$, $x = -17$, $x = -21$, and $x = -25$.
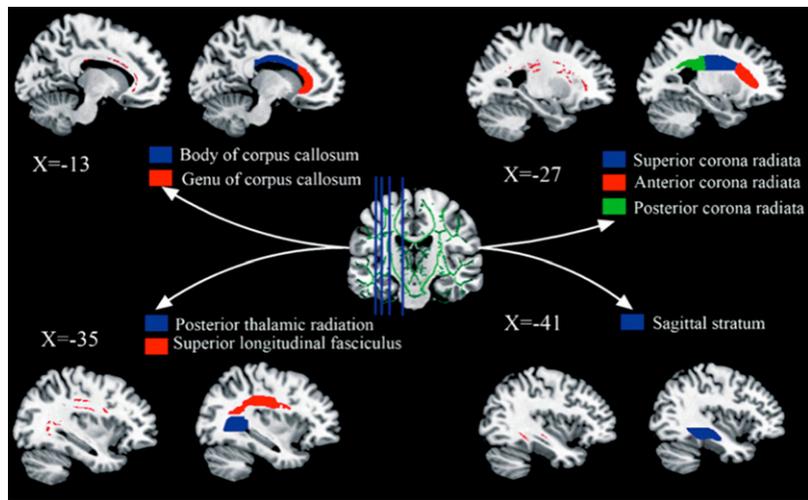
Tang et al.

Fig. 2. Decrease of AD in different brain regions after 2-wk IBMT. Statistical images are shown at $P_{FWE} < 0.05$ corrected for multiple comparisons at sagittal section $x = -13$, $x = -27$, $x = -35$, and $x = -41$.

IBMT, there was only a decrease in AD but no significant change in FA or RD. Only after 4 wk of training did we find a change in RD and FA. These findings, together with the early changes of AD in development (10), suggest that axonal morphology might be an early biomarker of white matter change. The different results at 2 and 4 wk could be a difference between Chinese and United States populations; however, in previous studies of the mechanism of IBMT we have found undergraduates in the two countries to have similar brain activity and white matter changes by IBMT (5, 16, 20). The average age in Chinese and American groups is 20-y old, and these undergraduates share similar interests, such as use of iPhones, computers, and the internet. We thought the Chinese students may be more sensitive to the meditation because of cultural influences, but did not find evidence of this. Until new studies provide a direct comparison, cultural or genetic differences between the two populations

remain possible explanations of the differences found between the 2- and 4-wk studies.

In a recent review, Zatorre et al. (9) proposed that myelination is regulated by axon diameter, and changes in axon diameter during learning could in turn cause oligodendrocytes to alter the thickness of the myelin sheath. Conversely, myelinating glia can regulate axon diameter and even the survival of axons (9). This evidence indicates that changes of myelination (indexed by RD) and axon diameter (indexed by AD) interact, and thus do not represent independent components of FA. However, this finding does not explain differences between training methods.

In animal studies, changes in central serotonin levels influence axonal morphology, suggesting emotions, such as stress and depression, have a negative effect on the axonal morphology (29, 30). Although few human experiments focus on the influence of emotions on axonal morphology, several studies have demonstrated that emotions and stress can change white matter integrity
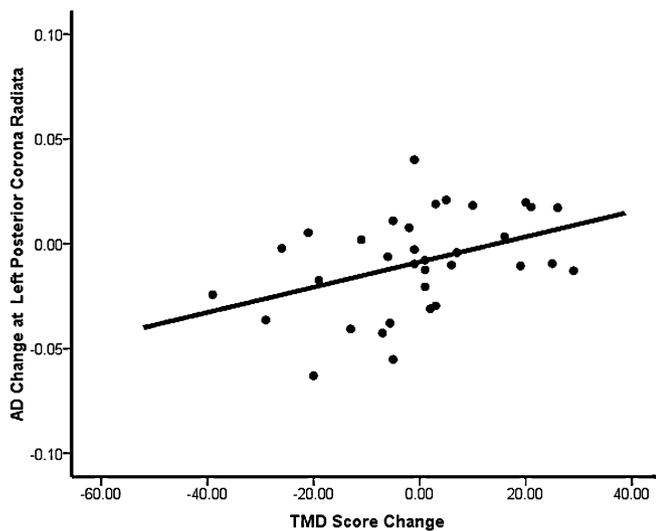

Fig. 3. Correlation between TMD change and AD decrease at left posterior corona radiata after 2-wk IBMT. The horizontal axis indicates the POMS total score change and the vertical axis indicates the AD change at left posterior corona radiata. A positive Pearson's correlation was observed ($r = 0.409$, $P = 0.016$).
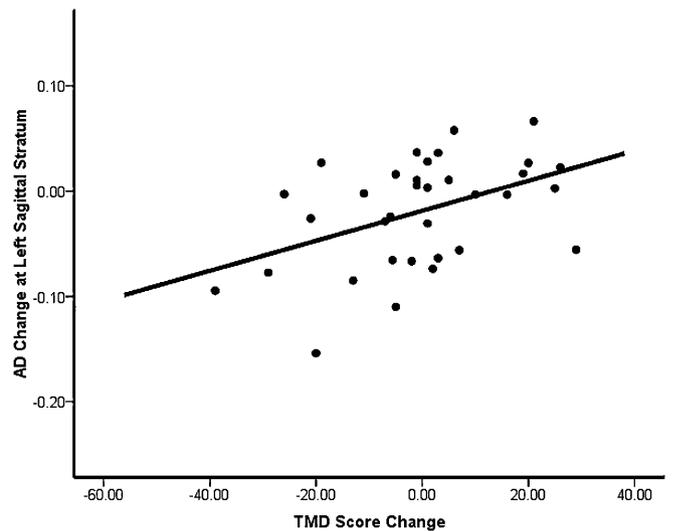

Fig. 4. Correlation between TMD change and AD decrease at left sagittal stratum ($r = 0.409$) after 2-wk IBMT. The horizontal axis indicates the POMS total score change and the vertical axis indicates the AD change at left sagittal stratum. A positive Pearson's correlation was observed ($r = 0.447$, $P = 0.008$).

Tang et al.

(31, 32). For example, the remission process of depression can enhance the FA near the anterior cingulate (32). After 1-wk IBMT, mood and positive emotion are enhanced (16, 19). Moreover, the FA increases found after 4 wk are in the corpus callosum, anterior corona radiata, and superior corona radiata (5), similar brain areas to those found in studies of white matter fibers influenced by emotion (31, 32). After 2-wk IBMT, positive correlations between POMS and AD changes are consistent with an important role for emotion. Thus, one possible explanation of AD changes might be that the training also has impacts on the autonomic nervous system and changing emotional state. The change of brain state and mood may be one reason for FA increase following IBMT practice (16, 17, 19, 20).

Wheeler-Kingshott and Cercignani (14) argued that the AD and RD may be problematic when either of the following conditions holds: (*i*) one has lower FA in brain regions, and (*ii*) crossing fibers make eigenvalue directions between subjects uncertain. We rule out these two conditions as follows: First, lower FA brain tissues, especially gray matter, have been removed from skeletonized FA, AD, and RD maps generating by the tract-based spatial statistics (TBSS) method so that the noise from low FA can be removed. Second, the longitudinal study design ensures each single voxel's eigenvalue directions are congruent in the pre- and posttraining scans because they came from same subject. Thus, it is unlikely the current results are noise or artifacts.

It should be noted that despite the controversy over the interpretation of AD and RD measures (14), diffusion-imaging measures are sensitive to many tissue properties (33), including variation in myelin (34), axon diameter and packing density (35), axon permeability (33), and fiber geometry (36). Diffusion imaging can be adapted to generate axon diameter distributions (37) or estimates of myelin microstructure (38). Such advances offer great potential to further our understanding of brain structural variation with learning and behavior (9).

In summary, our results demonstrate the mechanism of white matter neuroplasticity during short-term meditation. These findings might serve as a vehicle for examining the behavioral consequences of different indices of white matter integrity, such as functional connectivity, FA, RD, and AD that occur both during learning, training, and development. Moreover, a number of problems, including addiction and mental disorders such as attention-deficit hyperactivity disorder, anxiety, depression, schizophrenia, and borderline personality disorder, involve problems of self-regulation (39). Thus, the dynamic pattern of white matter change involving the ACC, a part of the brain network related to self-regulation, could provide a means for intervention to improve or prevent mental disorders.

Materials and Methods

Participants. In study 1, 45 healthy undergraduates [28 male, mean age 20.58 ± 1.57 (SD) y] at the University of Oregon were recruited and randomly assigned to an IBMT group or a relaxation group. Each group had no previous training experience and received 30 min of IBMT or RT for 1 mo, with a total of 11 h of training (5). In study 2, 68 healthy Chinese undergraduates [36 male, mean age 20.52 ± 1.36 (SD) y] at Dalian University of Technology were recruited and randomly assigned to an IBMT group or a relaxation group (34:34, 18 males in each group). The participants had no previous training experience and received 30 min of IBMT or RT for 2 wk, with a total of 5 h of training. The experiment was approved by the Institutional Review

Board at University of Oregon and Dalian University of Technology and informed consent was obtained from each participant.

Training Methods. IBMT involves body relaxation, mental imagery, and mindfulness training, accompanied by selected music background. Cooperation between the body and the mind is emphasized in facilitating and achieving a meditative state. The trainees concentrated on achieving a balanced state of body and mind guided by an IBMT coach and the compact disk. The method stresses no effort to control thoughts, but instead a state of restful alertness that allows a high degree of awareness of body, mind, and external instructions (5, 16, 19). RT involves the relaxing of different muscle groups over the face, head, shoulders, arms, legs, chest, back, and abdomen, guided by a tutor and compact disk. With eyes closed and in a sequential pattern, one is forced to concentrate on the sensation of relaxation, such as the feelings of warmth and heaviness. This progressive training helps the participant achieve physical and mental relaxation and calmness.

Data Acquisition and Analysis. In study 1, diffusion tensor images were collected twice, once before and once after 4-wk training on a Siemens 3T scanner at the Lewis Center for Neuroimaging, University of Oregon. The imaging parameters were as follows: TR/TE = 10,900/113 ms, diffusion-weighting gradients applied in 60 directions (b = 700 s/mm^2), combined 10 volumes without diffusion weighting (b = 0 s/mm^2).

In study 2, DTI scans were preformed twice, once before and once after 2-wk training with a Philips 3T Achieva at Dalian Municipal Central Hospital. DTI acquisition parameters were as follow: TR/TE = 10,815/62 ms, diffusion sensitizing gradient was applied along 29 directions (b = 1,000 s/mm^2) with one volume without diffusion weighting (b = 0 s/mm^2).

DTI data were processed with the FSL 4.1 Diffusion Toolbox (FDT, http://www.fmrib.ox.ac.uk/fsl/fdt/). A standard FDT multistep procedure was adopted including: (*i*) motion and eddy current correction; (*ii*) removal of skull and nonbrain tissue using the Brain Extraction Tool; and (*iii*) voxel-by-voxel calculation of the diffusion tensors. FA and AD maps calculated directly using DTIFit within FDT. The RD map was computed as the mean of the second and third eigenvalue with an in-house program. TBSS was carried out for voxelwise statistical analysis and included: (*i*) nonlinear alignment of each participant's FA volume to the standard Montreal Neurological Institute (MNI152) space template; (*ii*) calculation of the mean of all aligned FA images; (*iii*) creation of a mean FA skeleton that represents the centers of all tracts common to all subjects; and (*iv*) projection of each subject's aligned FA image onto the mean FA skeleton. The tbss_non_FA script was used to obtain: (*i*) the individual's projected template; (*ii*) calculation of the mean of all aligned FA images; (*iii*) creation of a mean FA skeleton that represents the centers of all tracts common to all subjects; and (*iv*) projection of each subject's aligned FA image onto the mean FA skeleton. The tbss_non_FA script was used to obtain the individual's projected AD and RD maps. Permutation-based nonparametric inference (http://www.fmrib.ox.ac.uk/fsl/randomise/) was adopted to perform statistical analyses on FA (n = 5,000), AD and RD in 2- and 4-wk IBMT and RT groups.

The statistical threshold was established as $P_{FWE} < 0.05$ with multiple comparison correction using threshold-free cluster enhancement (http://www.fmrib.ox.ac.uk/analysis/research/tfce). An in-house program was used to calculate the volume of AD or RD alterations within the regions where FA changes (40–43). Using the FSL Toolbox in all studies, we conducted *t* tests for pre- and posttraining differences with a correction for multiple comparisons ($P_{FWE} < 0.05$). Pearson correlation was also conducted to analyze correlation between imaging metrics and behavioral assessments.

1. Taubert M, Villringer A, Ragert P (2011) Learning-related gray and white matter changes in humans: An update. *Neuroscientist*, 10.1177/1073858411419048.
2. Hu Y, et al. (2011) Enhanced white matter tracts integrity in children with abacus training. *Hum Brain Mapp* 32:10–21.
3. Keller TA, Just MA (2009) Altering cortical connectivity: Remediation-induced changes in the white matter of poor readers. *Neuron* 64:624–631.
4. Engvig A, et al. (2011) Memory training impacts short-term changes in aging white matter: A longitudinal diffusion tensor imaging study. *Hum Brain Mapp*, 10.1002/hbm.21370.
5. Tang YY, et al. (2010) Short-term meditation induces white matter changes in the anterior cingulate. *Proc Natl Acad Sci USA* 107:15649–15652.
6. Burzynska AZ, et al. (2010) Age-related differences in white matter microstructure: Region-specific patterns of diffusivity. *Neuroimage* 49:2104–2112.
7. Bosch B, et al. (2012) Multiple DTI index analysis in normal aging, amnestic MCI and AD. Relationship with neuropsychological performance. *Neurobiol Aging* 33:61–74.
8. Bennett IJ, Madden DJ, Vaidya CJ, Howard DV, Howard JH, Jr. (2010) Age-related differences in multiple measures of white matter integrity: A diffusion tensor imaging study of healthy aging. *Hum Brain Mapp* 31:378–390.

9. Zatorre RJ, Fields RD, Johansen-Berg H (2012) Plasticity in gray and white: Neuro-imaging changes in brain structure during learning. *Nat Neurosci* 15:528–536.

10. Kumar R, Nguyen HD, Macey PM, Woo MA, Harper RM (2012) Regional brain axial and radial diffusivity changes during development. *J Neurosci Res* 90:346–355.

11. Kumar R, Macey PM, Woo MA, Harper RM (2010) Rostral brain axonal injury in congenital central hypoventilation syndrome. *J Neurosci Res* 88:2146–2154.

12. Song SK, et al. (2002) Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 17:1429–1436.

13. Song SK, et al. (2003) Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage* 20:1714–1722.

14. Wheeler-Kingshott CAM, Cercignani M (2009) About "axial" and "radial" diffusivities. *Magn Reson Med* 61:1255–1260.

15. Metwalli NS, et al. (2010) Utility of axial and radial diffusivity from diffusion tensor MRI as markers of neurodegeneration in amyotrophic lateral sclerosis. *Brain Res* 1348:156–164.

16. Tang YY (2011) Mechanism of integrative body-mind training. *Neurosci Bull* 27:383–388.

17. Tang YY, Posner MI (2009) Attention training and attention state training. *Trends Cogn Sci* 13:222–227.

18. Mori S, Wakana S, van Zijl PC, Nagae-Poetscher LM (2005) *MRI Atlas of Human White Matter* (Elsevier Science, Amsterdam, The Netherlands).

19. Tang YY, et al. (2007) Short-term meditation training improves attention and self-regulation. *Proc Natl Acad Sci USA* 104:17152–17156.

20. Tang YY, et al. (2009) Central and autonomic nervous system interaction is altered by short-term meditation. *Proc Natl Acad Sci USA* 106:8865–8870.

21. Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 4:215–222.

22. Niogi S, Mukherjee P, Ghajar J, McCandliss BD (2010) Individual differences in distinct components of attention are linked to anatomical variations in distinct white matter tracts. *Front Neuroanat* 4:2.

23. Fields RD (2010) Neuroscience. Change in the brain's white matter. *Science* 330:768–769.

24. Fields RD (2008) White matter in learning, cognition and psychiatric disorders. *Trends Neurosci* 31:361–370.

25. Holzel BK, et al. (2011) How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. *Perspect Psychol Sci* 6:537–559.

26. Rueda MR, Rothbart MK, McCandliss BD, Saccomanno L, Posner MI (2005) Training, maturation, and genetic influences on the development of executive attention. *Proc Natl Acad Sci USA* 102:14931–14936.

27. Rueda MR, Checa P, Combita LM (2012) Enhanced efficiency of the executive attention nentwork after training in preschool children: Immediate and after two month effects. *Developmental Cognitive Neuroscience* 2:192–204.

28. Tyszka JM, Readhead C, Bearer EL, Pautler RG, Jacobs RE (2006) Statistical diffusion tensor histology reveals regional dysmyelination effects in the shiverer mouse mutant. *Neuroimage* 29:1058–1065.

29. Liu Y, Nakamura S (2006) Stress-induced plasticity of monoamine axons. *Front Biosci* 11:1794–1801.

30. Kitayama I, et al. (1997) Long-term stress degenerates, but imipramine regenerates, noradrenergic axons in the rat cerebral cortex. *Biol Psychiatry* 42:687–696.

31. Chen L, et al. (2011) Impact of acute stress on human brain microstructure: An MR diffusion study of earthquake survivors. *Hum Brain Mapp*, 10.1002/hbm.21438.

32. Alexopoulos GS, et al. (2008) Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatry* 165:238–244.

33. Beaulieu C (2009) The biological basis of diffusion anisotropy. *Diffusion MRI: From Quantitative Measurement to in-Vivo Neuroanatomy*, eds Johansen-Berg H, Behrens TEJ (Elsevier, London), pp 105–126.

34. Concha L, Livy DJ, Beaulieu C, Wheatley BM, Gross DW (2010) In vivo diffusion tensor imaging and histopathology of the fimbria-fornix in temporal lobe epilepsy. *J Neurosci* 30:996–1002.

35. Takahashi M, et al. (2002) Magnetic resonance microimaging of intraaxonal water diffusion in live excised lamprey spinal cord. *Proc Natl Acad Sci USA* 99:16192–16196.

36. Wedeen VJ, Hagmann P, Tseng WY, Reese TG, Weisskoff RM (2005) Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magn Reson Med* 54:1377–1386.

37. Barazany D, Basser PJ, Assaf Y (2009) In vivo measurement of axon diameter distribution in the corpus callosum of rat brain. *Brain* 132:1210–1220.

38. Avram AV, Guidon A, Song AW (2010) Myelin water weighted diffusion tensor imaging. *Neuroimage* 53:132–138.

39. Posner MI (2012) *Attention in the Social World* (Oxford Univ Press, New York).

40. Smith SM, et al. (2006) Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31:1487–1505.

41. Smith SM, et al. (2004) Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 23(Suppl 1):S208–S219.

42. Rueckert D, et al. (1999) Nonrigid registration using free-form deformations: Application to breast MR images. *IEEE Trans Med Imaging* 18:712–721.

43. Smith SM, Nichols TE (2009) Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage* 44:83–98.

NEUROSCIENCE

Tang et al.