Major Depression Impairs Biophysical Integrity of Brain beyond Normal Aging Revealed by Magnetization Transfer Imaging

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Introduction

Normal aging is accompanied by brain atrophy and increased white matter hyperintensities (WMH) [1]. Similarly, volumetric decrease of (pre)frontal lobe and increased WMH in deep white matter have been consistently identified in patients with major depressive disorder (MDD) [2-3]. In addition, both MDD and aging are associated with microstructural changes such as lower fractional anisotropy (FA) in specific white matter tracts [4] or focal brain regions [5]. While the above findings represent some dimensions of the neurobiological abnormalities of MDD and aging, additional or supplementary MRI based methods are needed to identify other, possibly more subtle biophysical abnormalities in MDD and aging. Magnetization transfer (MT) is a MRI method that provides estimates of myelin and axonal density in white matter and protein and cell membrane composition in gray matter [6-8]. In this report, we examined the biophysical integrity of the brain using magnetization transfer ratio (MTR) imaging on patients with MDD and nondepressed comparison controls in a relatively large age range. We found that MTR declined with age in focal brain regions in both groups; however, the MDD group had additional brain regions showing significant decline of MTR with age. These findings suggest MDD and increasing age in combination are associated with more striking and extensive biophysical changes in the brain than normal aging alone.

Materials and Methods

Twenty-eight patients with MDD and 31 nondepressed comparison controls, ranging in age from 30 to 88, were recruited for this study from relevant clinics at the local area community. Consent forms had been acquired from all subjects. The patients with MDD met current clinical standards for a diagnosis of depression as determined by formal clinical interview, psychiatric evaluation, medical record review and laboratory testing, met the DSM-IV criteria for MDD, and required a score of 16 or higher on the 17-item HAM-D score.

The MRI scans were performed on a Philips Achieva 3T scanner with a SENSE-Head-8 coil. The MT images were acquired using a three-dimensional spoiled gradient-echo echo-planar imaging sequence. The sequence parameters are TR/TE = 64/15 ms, flip angle = 9°, FOV = 24 cm, 67 axial slices, slice thickness = 2.2 mm/no gap, off-resonance frequency of the RF pre-saturation pulse=1500 Hz [9,10]. The regions of interest (ROIs) as implicated important in the circuitry of depression were placed in the periventricular frontal white matter (pvFWM), head of caudate nucleus (hCaud), putamen, thalamus, globus pallidus, anterior cingulate cortex (ACC), lateral orbitofrontal cortex (lOFC), dorsolateral prefrontal cortex (DLPFC) in both hemispheres.

Differences in MTRs between the 2 groups were assessed using analysis of covariance (ANCOVA) controlling for age and sex. The significant level was set at 0.05. Correlations between the MTR and age were analyzed using partial Pearson's product-moment correlations controlling for the CES-D score, with Bonferroni correction for multiple comparisons set to p=0.003. All statistical analyses were carried out using SPSS version 18.

Results and Discussion

The two groups did not differ in age ($F_{1,57}$=0.11, p=0.75) and gender (χ^2=0, p=0.99). The MDD group had significantly higher HAM-D and CES-D scores (reflective of the severity of depression) than the control group (p<0.001 for both scores). The MTR in the right hCaud was significantly lower in the MDD group ($F_{1,55}$=7.75, p=0.007), compared with the control group. The MTR was not significantly different between groups in the other ROIs (p>0.06 for all the other regions). The MTR was negatively correlated with age in multiple brain regions shared by both groups. In the control group, the regions included left pvFWM, right DLPFC, and bilateral putamen (0.003<p<0.009 for all these regions) but no regions survived the Bonferroni correction for multiple comparisons set to p=0.003. In the MDD group, more regions showed negative correlation between MTR and age, which include bilateral hCaud, bilateral pvFWM, DLPFC and putamen, left ACC, and right globus pallidus (p<0.022 for all these regions). In the above regions in the MDD group, right hCaud (r=-0.585, p=0.002) and left putamen (r=-0.585, p=0.002) survived the Bonferroni correction for multiple comparisons set to p=0.003 (see Fig. 1).

The findings demonstrate that both MDD and normal aging are associated with age-related MTR decline in focal brain regions. However, MDD tends to accelerate the biophysical changes in some of those shared brain regions and/or the regions in the respective opposite hemispheres, such as putamen, DLPFC, and pvFWM. Moreover, MDD is also associated with the age-related MTR changes in additional brain regions such as right hCaud. These findings suggest MDD impairs the biophysical integrity of the human brain beyond normal aging and indicate an important subcortical biophysical component to major depression.

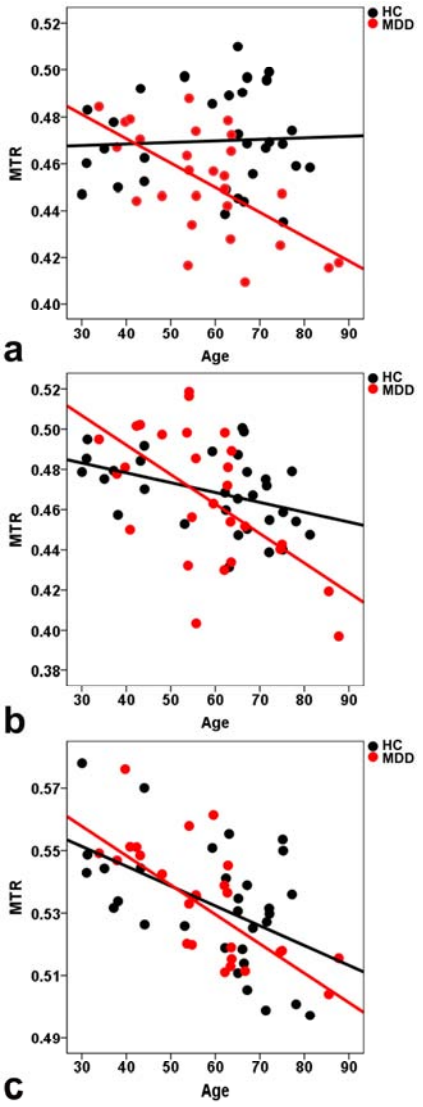

Fig. 1. Correlation of MTR and age, controlling for the CES-D score, in the control (HC) and MDD groups in (a) right hCaud (HC: r=0.024, p=0.896; MDD: r=-0.585, p=0.002), (b) left putamen (HC: r=-0.483, p=0.007; MDD: r=-0.585, p=0.002), and (c) left pvFWM (HC: r=-0.472, p=0.008; MDD: r=-0.521, p=0.006). Only right hCaud and left putamen in the MDD group survived the Bonferroni correction for multiple comparisons set to p=0.003.

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