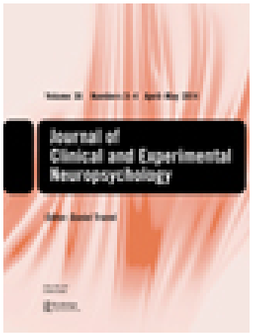

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Coping style as a protective factor for emotional consequences of structural neuropathology in multiple sclerosis

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ABSTRACT

Introduction: In people with multiple sclerosis (MS), depression symptoms could be a direct consequence of neuropathological processes or a secondary consequence of coping with debilitating illness. We investigated the interaction of white matter structure and patient coping style in predicting positive and negative emotion symptoms of depression.

Method: Participants completed a neuropsychological battery, including the Chicago Multiscale Depression Inventory (CMDI) and a measure of coping strategies that has Active Coping (more adaptive) and Avoidant Coping (less adaptive) scales. Participants also completed a diffusion tensor imaging (DTI) scan, from which fractional anisotropy (FA) was calculated to assess integrity in tracts of interest, and the interaction of FA and coping style was analyzed to predict depression symptoms.

Results: Significant FA and Active Coping interaction effects for predicting CMDI Negative Emotion scores were found for the anterior thalamic radiation and uncinate fasciculus white matter tracts. For people with MS who showed relatively reduced integrity of these tracts, use of more Active Coping moderated the relationship of microstructure and negative emotion symptoms of depression. This moderating relationship was not seen with other tracts of interest or with positive emotion.

Conclusion: There was a protective effect of adaptive coping style against the experience of negative emotion among people with MS who showed compromised regional white matter integrity of certain tracts that connect temporal and thalamic regions to frontal cortex.

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Affective symptoms; depression; emotion; neuroimaging; white matter

The pathophysiology of multiple sclerosis (MS), with chronic inflammation, demyelination and degeneration of axon fibers, and formation of lesions in the central nervous system (Kawachi & Lassman, 2017), results in focal and widespread effects on neural functioning and behavior. Consequences commonly include physical, cognitive, and emotional disability. Thus, research with this population can contribute to understanding of how different types of information, including emotional information, are processed in neural networks and the role of neuropathology in outcomes for people with debilitating neurological illness. Emotion disturbance is of particular importance in MS due to its frequent occurrence–lifetime prevalence of depression in MS is as high as 50% (Chwastiak et al., 2002; Sadovnick et al., 1996) and point prevalence approximately 25–40% (Feinstein, Magalhaes, Richard, Audet, & Moore, 2014). In comparison, depression occurs in approximately 8% of the general population (American Psychiatric Association, 2013), and additional research indicates that among chronic illnesses, depression is particularly prevalent in MS (Holden & Isaac, 2011). Depression in MS may be independent from the disease, directly related to physiological disease processes, or a secondary consequence of functioning with a chronic debilitating illness (Minden, 2000). Despite the prevalence, few studies have examined neurophysiological correlates of emotional problems in MS.

Depression has long been characterized as a disorder of both dimensions of positive and negative emotion, in which experience of negative emotions is increased and experience of positive emotions is decreased (Watson, Clark, & Carey, 1988). Negative emotion relates to feelings of fear, disgust, hostility, and sadness while positive emotion reflects feelings of enthusiasm, alertness, interest, and joy. Key criteria in diagnosis of major depressive disorder include experiences related to negative emotion, including sadness, while the anhedonia criterion relates to lack of positive emotion experiences (American Psychiatric Association, 2013; Bracht, Linden, &

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Keedwell, 2015). Examination of specific dimensions of depression may further clarify biological and environmental mechanisms contributing to expression of this heterogeneous disorder, and anhedonia in particular has been considered a possible endophenotype of depression (Pizzagalli, 2015). Depression research with MS populations has not often addressed distinctions between increased negative emotion and decreased positive emotion that may contribute to overall symptoms of depression. For example, one study of the effects of psychotherapy on improvement in depression in people with MS demonstrated that changes in overall symptom levels following the treatment were mediated by ratings of positive emotion (Hart, Vella, & Mohr, 2008).

While neurophysiological changes of MS could directly impact emotional functioning, additional psychosocial factors could also provide a moderating role. Coping is a conscious process for management of stressors (Somerfield & McCrae, 2000). In the self-regulation model of coping styles, active coping refers to a set of typically adaptive strategies for taking action, planning a response, seeking social support, suppressing attention to competing activities, and exercising restraint from acting prematurely, while avoidant coping is composed of typically less adaptive strategies associated with denial, focus on and venting of emotions, and behavioral and mental disengagement from goal attainment (Carver, Scheier, & Weintraub, 1989). In people with MS, coping style appears to contribute to increased depression symptoms and worse overall quality of life across a range of disease severity and diagnosis duration (Brands et al., 2017; Calandri, Graziano, Borghi, & Bonino, 2017). Coping style has been demonstrated to moderate variables that predict functional outcome in MS (Ukueberuwa & Arnett, 2014), including interactions between cognitive functioning and active and avoidant coping in predicting depression (Arnett, Higginson, Voss, Randolph, & Grandey, 2002; Rabinowitz & Arnett, 2009).

Neuropathology of MS involves demyelination and lesions in cell bodies and axon tracts in the brain (Kawachi & Lassman, 2017). Although diagnosis of MS relies mostly on clinical features, laboratory tests such as magnetic resonance imaging (MRI) now supplement the diagnostic process (Polman et al., 2011). MRI detects the location of lesions in the central nervous system that are characteristic of MS. While it continues to develop as a research and clinical tool, and at present is not typically used in diagnosis, diffusion tensor magnetic resonance imaging (DTI) can be used to quantify the microstructural characteristics of axon tracts (Marquez de la Plata et al., 2011). Fractional anisotropy (FA) is a measure of anisotropic diffusion through axon fibers, with higher FA values appearing in regions with highly organized axonal tracts with greater microstructural integrity (Beaulieu, 2002). Thus, decreased FA could be a biomarker of diffuse axonal injury or lesions in fibers (Marquez de la Plata et al., 2011). FA diffusion maps indicate regions of higher and lower FA across the whole brain or specific regions of interest. In postmortem comparison studies of individuals with MS, FA was correlated with myelin content and axon count in normal-appearing white matter and white matter lesions (Schmierer et al., 2007).

Although a direct causal relationship is unclear, further research may demonstrate whether axonal damage alters neural activity and behavior. Tracts connecting regions that are involved in networks for processing experience of emotion could be disrupted in people who show elevated negative emotion or low positive emotion. A previous study of group differences between depressed and nondepressed individuals with MS found that DTI measures within broad temporal and prefrontal regions predicted group status, with reduced microstructural integrity of these regions in the depressed group (Feinstein et al., 2010). Previous DTI studies of major depression in otherwise healthy people have largely demonstrated reduced FA in frontal and temporal regions, as well as in the anterior cingulate cortex, the thalamus (e.g., anterior thalamic radiation, anterior limb of internal capsule), and the uncinate fasciculus tract, which connects lateral orbitofrontal cortex to the anterior temporal lobe (Bracht et al., 2015; Sexton, Mackay, & Ebmeier, 2009). Axon tracts associated with reward systems, theoretically related to positive emotional experiences, include the inferior frontal occipital fasciculus, cingulum bundle, and corpus callosum (Camara, Rodriguez-Fornells, & Munte, 2010; Koch et al., 2013). FA values in these tracts positively correlated with blood-oxygen-level-dependent (BOLD) signal response (e.g., an index of neural activity) in the ventral striatum during reward processing. The anterior thalamic radiation, anterior limb of the internal capsule, and uncinate fasciculus have been variably associated with both the reward system and stress systems related to negative emotional experience (Bracht et al., 2015; Camara et al., 2010). Functional brain imaging studies of people with depression who do not have neurological illness indicate a network of regions that play a role in the occurrence of depression symptoms. These studies consistently show involvement of the prefrontal cortex, along with other connected cortical and subcortical regions (Mayberg, 2006).

Despite these studies, the literature specifically using neuroimaging to examine relationships between neural structure and emotion functioning in people with MS

remains limited. The present study investigated the following hypotheses: (a) Reduced white matter microstructural integrity will predict maladaptive emotional symptoms (high negative emotion, low positive emotion); furthermore, we expect divergence between the white matter regions that are correlated with negative and positive emotion dimensions. Given available literature reviewed above, FA in the inferior frontal occipital fasciculus and cingulum bundles are expected to correlate with positive emotion. FA in anterior thalamus and uncinate fasciculus are expected to correlate with negative emotion. (b) Coping style will moderate the relationship between microstructural integrity and emotion. Specifically, patients with lower white matter integrity, either across the brain or in particular tracts previously associated with depression and reward, who used overall more active coping or less avoidant coping, will show emotional function comparable to that of patients with higher white matter integrity.

Method

Participants and procedures

Participants were recruited through flyers posted in the community and an advertisement placed in the Central Pennsylvania Chapter of the National Multiple Sclerosis Society MS Connection newsletter. Inclusion criteria were adults with diagnosis of MS. Interested participants completed a telephone interview in order to determine eligibility. Diagnoses were clinically confirmed using Polman et al. (2011) criteria. Neurological impairment was rated with the Expanded Disability Status Scale (EDSS) during a neurological exam. Exclusionary criteria were history of nervous system disorder other than MS, other medical condition that could substantially affect cognition or motor function, severe physical or sensory impairments that might significantly interfere with cognitive testing, alcohol/drug abuse, or developmental history of a learning disability or attention-deficit/hyperactivity disorder. Patients were also excluded for experience of disease relapse or corticosteroid use within four weeks prior to the scheduled assessment. Patients were not excluded for use of antidepressant or antianxiety medications. Fifty-three participants met the inclusion/exclusion criteria. Five participants were excluded from DTI analysis due to changes in their scanning protocol (i.e., shortened scans due to patient discomfort) or corruption of resulting images due to excessive movement, resulting in a final sample of 48 participants. Sample characteristics are reported in Table 1. Measures for this study were administered within a larger battery of neuropsychological tests, self-report measures of psychosocial functioning, and neuroimaging scans for a study of depression in MS. All participants received $100 compensation and a clinical neuropsychological evaluation report. The study was approved by the university's Institutional Review Board.

Table 1. Demographic and MS disease characteristics for participants.

	Participants (N = 48)	
	M (SD)	%
Age (years)	53.15 (11.55)	
Education (years)	14.75 (2.00)	
Diagnosis duration (years)	17.04 (8.76)	
Expanded Disability Status Scale	4.43 (1.53)	
Shipley–2 standard score	98.92 (14.01)	
Beck Depression Inventory–Fast Screen	3.17 (3.88)	
Cutoff ≥4 (%)	2.92	
Sex		
Female		68.8
Male		31.3
MS course type		
Relapsing-remitting		72.9
Secondary progressive		20.8
Primary progressive		4.2
Progressive-relapsing		2.1

Note. MS = multiple sclerosis.

Neuropsychological measures

The Shipley-2 was used to measure general intellectual functioning (Shipley, Gruber, Martin, & Klein, 2009). The total standard score combines subscores for vocabulary and abstract problem-solving skill.

The Beck Depression Inventory–Fast Screen (BDI–FS) was used to evaluate severity of depressive symptoms (Beck, Steer, & Brown, 2000). A total score of greater than or equal to four indicates significant symptoms (Steer, Cavalieri, Leonard, & Beck, 1999). This questionnaire has been validated for assessment of depression in MS (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003; Strober & Arnett, 2015).

Negative and positive emotion were evaluated with the Chicago Multiscale Depression Inventory (CMDI). The 5-point Likert scale self-report measure was designed and validated for measurement of depression in medical populations (Nyenhuis et al., 1998). In this study, summed scores from the CMDI Mood and Evaluative symptom scales were used as an index of Negative Emotion. A CMDI Positive Emotion symptom scale was also recently validated by the authors (Ukueberuwa & Arnett, 2015), and it was used here as an index of positive emotion. In that article we reported that MS patients in this sample were elevated on Mood and Evaluative scales and lower on the Positive Emotion scale compared to a sample of demographically matched healthy adult

controls. The *t*-scores on CMDI scales were presently calculated based on demographically matched healthy control data previously reported in Ukueberuwa and Arnett (2015).

The COPE is a validated measure of strategies that impede or contribute to adaptive coping in response to stress (Carver et al., 1989), with two subscales relating to active and avoidant coping. The Active Coping scale includes items related to active coping, planning, and suppression of competing activities. The Avoidant Coping scale includes items related to behavioral disengagement, mental disengagement, and denial.

Neuroimaging protocol

MRI of the brain was performed on a 3-Tesla Siemens Magneto Trio A Tim System. High-resolution structural T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sagittal images were acquired (1-mm isotropic resolution; time to repetition, TR, 1650 ms; echo time, TE, 2.03 ms; 9° flip angle; 250-cm field of view; 1-mm slice thickness). DTI was conducted in order to measure the microstructural integrity of neural tracts. The DTI sequence included the following parameters: TR 8700 ms, 89 ms, 66 slices, slice thickness 2 mm contiguous, 30 directions, B = 1000 s mm^{-2} with two non-diffusion-weighted baseline images (B = 0 s mm^{-2}). Participants were lying supine in the scanner. Cushioning was used to stabilize the head within the coil to reduce motion-induced signal degradation.

DTI analysis

DTI measures were analyzed using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL). Diffusion-weighted images were first inspected for quality and artifacts, followed by preprocessing with the FSL Diffusion Toolbox: brain extraction, eddy current correction, and estimation of diffusion tensors. Tract-based spatial statistics (TBSS) was used to measure voxel-wise fractional anisotropy, the strength and directionality of local tract microstructure. The steps in TBSS included nonlinear registration of each participant's FA image to standard space. For study of a clinical population with neuropathology, each image was aligned to the most representative image in the sample rather than use of a standard template. Registration was followed by creation of a mean FA skeleton map from the sample, with an intensity threshold of 0.2. The resulting FA skeleton mask was then used for voxel-wise statistics. Whole brain and regional (fronto-temporal-subcortical) functional anisotropy (FA) were the primary indices derived from DTI processing.

Statistical analysis

Whole brain and regional voxel-wise statistics were conducted with TBSS to measure the relationship between FA, a measure of axon tract microstructure, and measures of positive and negative emotion. Five FA regions of interest were selected based on structures associated with depression and reward systems in the above-reviewed literature: anterior thalamic radiation, cingulum bundle–cingulate gyrus, cingulum bundle–hippocampus, inferior frontal-occipital fasciculus, and uncinate fasciculus. These white matter structures were then defined by the Johns Hopkins University White Matter Tractography Atlas. Masks were constructed for each region, and then FA values were calculated within the mask for each participant.

Additional descriptive statistics, correlation, and multiple regression analyses were then completed using IBM SPSS Statistics 22. Demographic and disease variables (e.g., age, education, diagnosis duration, EDSS) were correlated with CMDI emotion scale scores to determine any covariates. Separate regression analyses were used to assess the main effects of whole brain and regional FA and main effects of each of the coping and stress variables, and the interaction effects, to predict emotion scales. Independent variables were assessed for normality and were entered in the linear regression model in the following steps: *(Step 1)* FA (mean or regional); *(Step 2)* Coping (Active or Avoidant); *(Step 3)* FA × Coping interaction term. The dependent variable was emotion (CMDI Positive or Negative Emotion).

Results

Consistent with previously reported findings, 29.2% of this sample of participants with MS endorsed significant emotional distress on a self-report measure of depression-related symptoms (BDI–FS). Mean depressive symptoms across the sample was within the normal range (M = 3.17, SD = 3.88).

Descriptive data of coping and emotion scales are reported in Table 2. Neither demographic nor disease variables were significantly correlated with CMDI scales (all $p > .05$), and thus no covariates were included in subsequent analyses. Correlations between the demographic and disease variables and the independent variables (e.g., FA and COPE scales) are reported in Table 3.

Table 2. Descriptive characteristics for psychological scales.

Scales	*M* (*SD*)	T
Active Coping	32.18 (7.56)	—
Avoidant Coping	20.62 (4.59)	—
CMDI Negative	42.79 (17.78)	55.98
CMDI Positive	27.65 (5.03)	46.30

Note. COPE Inventory (COPE) coping style (Active Coping, Avoidant Coping raw scores) and Chicago Multiscale Depression Inventory (CMDI) emotion symptoms (CMDI Negative emotion, CMDI Positive emotion raw scores and *t*-scores).

In order to determine a relationship between white matter microstructural integrity and emotion, mean whole brain FA was calculated across all participants and then correlated with the CMDI subscales. There were no significant ($p < .05$) correlations between mean whole brain FA and either of the CMDI Scales, Negative or Positive. Voxel-wise whole brain FA analysis (TBSS) also did not reveal significant clusters for a relationship between FA and Negative or Positive emotion scales. Thus, results did not indicate a linear relationship between FA measures of microstructural disease characteristics and scores on the CMDI emotion subscales.

Emotional functioning in MS could also reflect adjustment to chronic debilitating illness. Further analyses were conducted to assess the interaction of FA and psychosocial variables of coping—Active and Avoidant Coping—in predicting emotional functioning, with the hypotheses that coping style would moderate the relationship between FA and emotion. Correlations between main and interaction terms are reported in Table 4.

Results indicated significant correlation between Active Coping and positive emotion ($r = .42$, $p < .01$), and significant correlations between Avoidant Coping and both positive emotion ($r = -.43$, $p < .01$) and negative emotion ($r = .63$, $p < .01$). There were no significant interaction effects between whole brain mean FA and coping variables for predicting the emotion scales. However, significant results, noted in Table 5, were obtained for certain white matter region of interest regression analyses. The interaction of anterior thalamic FA and Active Coping predicted 26% of the variance in CMDI Negative Emotion, $\Delta F(1, 41) = 7.15$, $\Delta R^2 = .13$, $p < .001$. In addition, the interaction of uncinate fasciculus FA and Active Coping predicted 22% of the variance in CMDI Negative Emotion, $\Delta F(1, 41) = 6.18$, $\Delta R^2 = .12$, $p < .001$. These interaction effects are displayed in Figure 1. Neither the interaction of anterior thalamic radiation FA nor that of uncinate fasciculus FA with Avoidant Coping was significant. Furthermore, there were no significant interactions in prediction of FA in the other regions of interest (cingulum bundle–hippocampus, cingulum bundle–cingulate gyrus, inferior frontal occipital fasciculus) with either coping variable in predicting CMDI Negative Emotion. There were also no significant interactions between any of the regional FA measures and either coping scale in predicting CMDI Positive Emotion.

Summary of negative interaction effects for predicting CMDI Positive Emotion: mean FA and Active Coping, $\Delta F(1, 41) = 2.10$, $\Delta R^2 = .04$, $p > .05$; mean FA and Avoidant Coping, $\Delta F(1, 41) = 0.38$, $\Delta R^2 = .01$, $p > .05$; anterior thalamic radiation FA and Active Coping, $\Delta F(1, 41) = 3.91$, $\Delta R^2 = .07$, $p > .05$; cingulum–cingulate gyrus FA and Active Coping, $\Delta F(1, 41) = 3.01$, $\Delta R^2 = .06$, $p > .05$; cingulum–cingulate gyrus FA and Avoidant Coping, $\Delta F(1, 41) = 0.23$, $\Delta R^2 = .00$, $p > .05$; cingulum–hippocampus FA and Active Coping, $\Delta F(1, 41) = 0.22$, $\Delta R^2 = .00$, $p > .05$; cingulum–hippocampus FA and Avoidant Coping, $\Delta F(1, 41) = 0.04$, $\Delta R^2 = .00$, $p > .05$; inferior fronto-occipital fasciculus FA and Active Coping, $\Delta F(1, 41) = 3.49$, $\Delta R^2 = .06$, $p > .05$; inferior fronto-occipital fasciculus FA and Avoidant Coping, $\Delta F(1, 41) = 1.53$, $\Delta R^2 = .02$, $p > .05$; uncinate fasciculus FA and Active Coping, $\Delta F(1, 41) = 3.89$, $\Delta R^2 = .07$, $p > .05$; uncinate fasciculus FA and Avoidant Coping, $\Delta F(1, 41) = 0.22$, $\Delta R^2 = .00$, $p > .05$.

Table 3. Correlation matrix for demographic variables, independent variables, and dependent variables.

1. Active COPE	1													
2. Avoidant COPE	−.16	1												
3. Whole brain FA	−.15	−.16	1											
4. Anterior thalamic radiation FA	−.18	−.31*	.77**	1										
5. Cingulum–cingulum FA	−.24	−.26	.80*	.94**	1									
6. Cingulum–hippocampus FA	−.10	−.26	.66**	.73**	.71**	1								
7. Interior fronto-occipital fasciculus FA	−.13	−.27	.80**	.96**	.93**	.75**	1							
8. Uncinate fasciculus FA	−.19	−.24	.74**	.94**	.89**	.70**	.95**	1						
9. Age	.33*	−.01	−.31*	−.34*	−.34*	−.16	−.37*	−.44**	1					
10. Education	.30*	−.04	.12	.05	.10	.10	.10	.03	−.04	1				
11. Diagnosis duration	.31*	−.08	−.39**	−.37**	−.31*	−.33*	−.39**	−.41**	.61**	−.11	1			
12. Expanded Disability Status Scale	.13	.13	−.43**	−.39**	−.43**	−.34	−.42**	−.38**	.29*	−.06	.24	1		
13. CMDI Positive Emotion	.42**	−.43**	−.13	.022	−.01	.05	.02	−.01	.11	.11	.12	−.15	1	
14. CMDI Negative Emotion	−26	.63**	.03	−.19	−.16	−.16	−.12	−.12	−.18	−.07	−.25	.16	−.59**	1

Note. FA = fractional anisotropy; COPE = COPE Inventory; CMDI = Chicago Multiscale Depression Inventory.
*Pearson correlation significant $p < .05$. **Pearson correlation significant $p < .01$.

Table 4. Correlations for independent variable main and interaction terms.

Active COPE interaction terms	Mean FA × Active COPE	Anterior thalamic radiation FA × Active COPE	Cingulum–cingulum FA × Active COPE	Cingulum–hippocampus FA × Active COPE	Interior fronto-occipital fasciculus FA × Active COPE	Uncinate fasciculus FA × Active COPE
Active COPE	.96**	.96**	.94**	.93**	.94**	.94**
Mean FA	.13	.07	.14	.11	.13	.11
Anterior thalamic radiation FA	−.08	.10	.15	.10	.14	.14
Cingulum–cingulum FA	−.02	.02	.11	.03	.08	.06
Cingulum–hippocampus FA	.09	.11	.16	.28	.16	.14
Interior fronto-occipital fasciculus FA	.10	.14	.20	.15	.21	.20
Uncinate fasciculus FA	.02	.07	.12	.07	.13	.15
Avoidant COPE	.95**	.95**	.93**	.91**	.93**	.93**
Mean FA	.14	.07	.14	.12	.13	.10
Anterior thalamic radiation FA	.10	−.01	.03	−.01	.04	.02
Cingulum–cingulum FA	.02	.02	.10	.03	.07	.05
Cingulum–hippocampus FA	−.06	−.05	−.01	.16	.00	−.02
Interior fronto-occipital fasciculus FA	−.03	.02	.07	.03	.09	.07
Uncinate fasciculus FA	−.02	.05	.09	.05	.11	.12

Note. FA = fractional anisotropy; COPE = COPE Inventory; CMDI = Chicago Multiscale Depression Inventory.
*Pearson correlation coefficient significant $p < .05$. **Pearson correlation coefficient significant $p < .01$.

Table 5. Significant interaction effects in regression analyses of regional fractional anisotropy and coping scale predicting negative emotion (dependent variable).

Regression	Entry order	Independent variables entered	β *(p)*	R^2	Δ*F*	Tolerance	*p*
1	Step 1	Anterior thalamic radiation FA	−1.93 (<.01)	.04	1.83	—	>.05
	Step 2	Active Coping	−6.35 (<.01)	.13	4.53	.97	<.05
	Step 3	FA × Coping interaction	5.98 (<.01)	.26	7.15	.99	<.001
2	Step 1	Uncinate fasciculus FA	−1.76 (<.01)	.02	0.76	—	>.05
	Step 2	Active Coping	−4.90 (<.01)	.10	4.06	.96	<.05
	Step 3	FA × Coping interaction	4.59 (<.01)	.22	6.18	.98	<.001

Note. FA = fractional anisotropy.

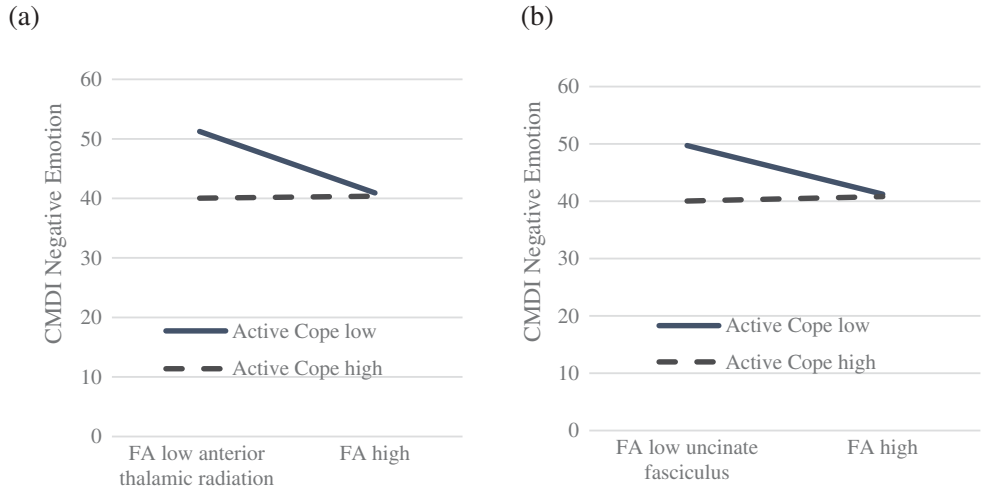

Figure 1. Graphs of significant interaction for fractional anisotropy (FA) values and coping style predicting Chicago Multiscale Depression Inventory (CMDI) emotion.

Summary of negative interaction effects for predicting CMDI Negative Emotion: mean FA and Active Coping, $\Delta F(1, 41) = 0.47$, $\Delta R^2 = .01$, $p > .05$; mean FA and Avoidant Coping, $\Delta F(1, 41) = 0.24$, $\Delta R^2 = .00$, $p > .05$; anterior thalamic radiation FA and Active Coping, $\Delta F(1, 41) = 2.19$, $\Delta R^2 = .03$, $p > .005$; cingulum–cingulate gyrus FA and Active Coping, $\Delta F(1, 41) = 4.63$, $\Delta R^2 = .09$, $p > .005$; cingulum–cingulate gyrus FA and Avoidant Coping, $\Delta F(1, 41) = 1.86$, $\Delta R^2 = .03$, $p > .05$; cingulum–hippocampus FA and Active Coping, $\Delta F(1, 41) = 1.15$, $\Delta R^2 = .02$, $p > .05$; cingulum–hippocampus FA and Avoidant Coping, $\Delta F(1, 41) = 3.66$, $\Delta R^2 = .05$, $p > .05$;

inferior fronto-occipital fasciculus FA and Active Coping, $\Delta F(1, 41) = 5.72$, $\Delta R^2 = .11$, $p > .005$; inferior fronto-occipital fasciculus FA and Avoidant Coping, $\Delta F(1, 41) = 0.00$, $\Delta R^2 = .00$, $p > .05$; uncinate fasciculus FA and Avoidant Coping, $\Delta F(1, 41) = 1.04$, $\Delta R^2 = .02$, $p > .05$.

Discussion

The present study was designed to examine neurophysiological and psychological factors related to emotional functioning in people with MS. Depression in particular is highly prevalent in this population; however, there are few published studies of the neurobiological factors related to depression or emotion in people with MS. Depression and disorders of positive and negative emotion are significant in their impact on daily functioning and in their relationship to other aspects of functioning such as cognitive ability (Arnett et al., 2002; Chwastiak et al., 2002; Holden & Isaac, 2011; Minden, 2000).

Initial predictions stated that measures of axon tract microstructure would be significantly correlated with measures of emotion, and that there would be nonoverlapping regions of interest that correlated with the positive and negative emotion scales. Results of this study did not support a direct relationship between measures of tract microstructure and self-reported emotion in people with MS, including in specific regions with reported associations to depression symptomology and reward processing. Instead, analyses indicated a moderating effect of coping style. In particular, use of more active coping was associated with decreased overall negative emotion symptoms. For people with MS who showed relatively reduced integrity in the anterior thalamic radiation and the uncinate fasciculus, use of more active coping moderated the relationship of microstructure and negative mood symptoms. These tracts provide a structural link between the temporal lobe and anterior thalamus with orbital and prefrontal cortex, respectively. Thus, these findings suggest that white matter microstructural changes may not directly contribute to the emotional problems seen in people with MS, but rather, personal factors such as coping style are important for managing mood symptoms. Previous work by our research group has demonstrated the robustness of coping style in predicting depression and psychological functioning in MS (Arnett et al., 2002; Rabinowitz & Arnett, 2009; Ukueberuwa & Arnett, 2014).

Findings and conclusions from these studies may be limited by certain characteristics of the sample and method. The emotion scales were derived from a measure validated for measurement of depression (CMDI). While the use of negative and positive dimensions separates some of the variance in factors that can contribute to elevated scores on depression scales, examination of additional factors such as personality traits and commonly comorbid symptoms (e.g., anxiety) may further clarify these relationships. In addition, many individuals with MS are prescribed antidepressants or other medications for mood changes, fatigue, adjustment problems, and other symptoms of the disease. As such, it was not considered feasible in the present study to exclude participants who were on such medications. However, these treatments could possibly affect neuropathology in an individual with history of depression. The MS patients in this sample had, on average, a moderate disability level, and thus the level of neuropathology may also be moderate; the range of FA values in patients with minimal, moderate, and severe disability has not presently been established. It is possible that a broader range of pathology would be necessary to further demonstrate differences between positive and negative emotion, which appear to have partially overlapping features. Furthermore, individuals with severe disability may on average have greater level of neuropathological change, and a direct relationship between structure and function could become more apparent with increased pathology.

The selection of regions of interest may have also limited these findings, in that it was primarily based on research literature about depression and emotion in otherwise healthy people due to greater prevalence of studies (Camara et al., 2010; Koch et al., 2013; Sexton et al., 2009). However, neural structures or mechanisms related to depression in people with MS may not fully parallel the mechanisms in healthy individuals. It will be useful to further research these neural networks and functional relationships in both healthy and MS populations. Finally, this study employed FA, one measure of white matter microstructural integrity, as the primary index of structural neuropathology. Further research regarding other structural measures (i.e., lesion burden, volumetric based morphology) will additionally inform the scope of the present findings.

Results of the present study did not clearly demonstrate different underlying structural or functional neural regions associated with dimensions of positive and negative emotion. Instead, this study demonstrated that coping style was an important predictor of emotional functioning in people with MS, and that coping can moderate the relationship between microstructural neuropathology and negative emotion. These findings emphasize the complex nature of emotional functioning in MS, which is related to neural, cognitive, and psychosocial factors. Finally, more information is

needed to clearly understand any division in functioning of positive and negative emotion systems.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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