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Dissociable Cognitive Patterns Related to Depression and Anxiety in Multiple Sclerosis

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Abstract

Background: Individuals with multiple sclerosis (MS) frequently present with depression and anxiety, as well as cognitive impairment, challenging clinicians to disentangle interrelationships among these symptoms.

Objective: To identify cognitive functions associated with anxiety and depression in MS.

Methods: Mood and cognition were measured in 185 recently diagnosed patients [Reserve Against Disability in Early Multiple Sclerosis (RADIEMS) cohort], and an independent validation sample (MEM CONNECT cohort, n=70). Partial correlations evaluated relationships of cognition to anxiety and depression controlling for age, sex, education, and premorbid verbal intelligence.

Results: In RADIEMS cohort, lower anxiety was associated with better nonverbal memory (r_p= −.220, p=.003) and lower depression to better attention/processing speed (r_p= −.241, p=.001). Consistently, in MEM CONNECT cohort, lower anxiety was associated with better nonverbal memory (r_p= −.271, p=.028) and lower depression to better attention/processing speed (r_p= −.367, p=.002). Relationships were unchanged after controlling for T2 lesion volume and fatigue.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest that directly relate to this work.

DATA SHARING

Data from both cohorts are available upon reasonable request to PIs (RADIEMS: Sumowski; MEM CONNECT: Leavitt).

Conclusion: Consistent mood-cognition relationships were identified in two independent cohorts of MS patients, suggesting that cognitive correlates of anxiety and depression are separable. This dissociation may support more precise models to inform treatment development. Treatment of mood symptoms may mitigate effects on cognition and/or treatment of cognition may mitigate effects on mood.

Keywords

anxiety; depression; cognition; multiple sclerosis; memory impairment

INTRODUCTION

Depression and anxiety each affect more than 20% of multiple sclerosis (MS) patients,[1] resulting in decreased quality of life,[2] altered health services utilization,[3] and emerging evidence showing increased hospitalizations and mortality[4] and worse disability progression.[5] Cognitive decline is another common and debilitating symptom of MS,[6] although patterns of deficits vary from patient to patient (i.e., cognitive phenotypes).[7] Clinicians are frequently challenged to disentangle whether / to what extent mood issues underlie or contribute to cognitive impairment. To our knowledge, there have been only three prior studies in the MS literature that evaluated relationships of both anxiety and depression in the same sample to cognitive functioning.[8-10] Given the high prevalence and pervasive impact of mood symptoms and cognitive impairment in MS, we aimed to replicate and extend these findings in the present study, which provides three key advancements: (1) replication in two independent samples of MS patients at different stages of disease (i.e., early, and later); (2) comprehensive cognitive evaluation and derivation of latent variables of cognition for more precise parcellation of specific cognitive functions; and (3) inclusion of a magnetic resonance imaging (MRI) measure of disease burden (i.e., T2 lesion volume).

Anxiety and depression are characterized by distinct clinical presentations, i.e., depression presents typically as anergia and dysthymia, anxiety as hypervigilance and restlessness. Based on this and the results of the aforementioned studies,[8,9,11] we hypothesized that we would find different cognitive functions related to anxiety and depression in the present study. Developing a more precise model of cognition-mood relationships may inform our approach to addressing / treating mood issues and cognition in MS.

MATERIALS AND METHODS

All study procedures were approved by local institutional review boards. Written informed consent was obtained from all participants prior to enrollment.

Participants.

Our investigation of mood-cognition relationships was conducted in two independent cohorts: the Reserve Against Disability in Early MS (RADIEMS) Cohort, and the MEM CONNECT cohort. RADIEMS is a longitudinal study of risk and protective factors for cognitive decline in persons aged 20 to 50 years and within five years of relapsing-remitting MS (RRMS) or clinically isolated syndrome diagnosis.[12] MEM CONNECT is a longitudinal

study examining candidate biomarkers to predict memory decline in adults aged 18-65 with RRMS. Baseline data for both studies were used here. Sample characteristics for both cohorts are displayed in Table 1.

Measurement of cognition.

In each cohort, participants completed a comprehensive neuropsychological battery of tasks assessing attention / information processing speed, verbal fluency, and memory (see descriptions below, Table 2). Performance on each task was regression-adjusted for age, sex, and estimated premorbid verbal ability as a proxy for IQ (WTAR). The cognitive battery administered in each cohort is described in detail. **RADIEMS Cohort**: (1) The Symbol Digit Modalities Test (SDMT) is a 90-second task wherein subjects orally provide digits that match visual symbols based on nine digit-symbol pairings in a key as quickly as possible. (2) WAIS-IV Digit Span is a task requiring subjects to repeat orallypresented strings of digits in forward, backward, or re-ordered sequences. (3) Stroop Color and Word Test (SCWT) requires subjects to (a) read the words (red, green, blue) written in black ink as quickly as possible for 45 seconds, (b) name the ink color (red, blue, green) of X's as quickly as possible for 45 seconds, and (c) name the ink color (red, green, blue) of non-matching printed words (e.g., "red" written in green ink) as quickly as possible for 45 seconds. (4) The NIH Toolbox Pattern Comparison task is a 90-second tablet-based task wherein subjects rapidly indicate via button press whether two presented pictures are the same or different. (5) The Phonemic Fluency (FAS) and Semantic Fluency (Animals) word generation tasks require subjects to quickly name as many words as possible starting with target letters across three 60-second trials (FAS) or belonging to a semantic category in one 60-second trial (Animals). (6) Verbal memory was assessed with the Selective Reminding Test (SRT), which requires subjects to learn 16 words across six trials and recall them after a delay; and a paired-associate learning task, Verbal Paired Associate Learning (V-PAL), requiring subjects to learn 12 unrelated word pairs across four trials and recall them after a delay. (7) Nonverbal memory was assessed with the Cambridge Neuropsychological Test Automated Battery Paired Associate Learning test (PAL; Cambridge Cognition, Cambridge, UK) task, which requires subjects to recall locations where visual stimuli were presented; total errors (TEA) and a memory score based on first guess (FAMS) are captured. The Brief Visuospatial Memory Test, Revised (BVMT-R), is a nonverbal (geometric shapes and locations) memory test of the Brief Repeatable Battery for MS. From these measures, fifteen variables were entered into a Principal Components Analysis (PCA, direct oblimin rotation), yielding four latent variables of cognition (Eigenvalues > 1.0). As shown in Table 2, these variables represent (1) Nonverbal memory, (2) Language / verbal fluency, (3) Verbal Memory, and (4) Attention / processing speed. **MEM CONNECT Cohort**: All tests were administered except for CANTAB PAL, VPAL, and NIH PC. Thirteen variables were entered into a PCA as above, yielding four latent variables of cognition (Eigenvalues > 1.0) broadly consistent with those derived in the RADIEMS cohort.

Measurement of anxiety and depression.

In the RADIEMS cohort, participants completed the Mental Health Inventory (MHI),[13] an 18-item scale including 5 items measuring anxiety (MHI-A) and 4 items measuring depression (MHI-D); the Beck Depression Inventory, Fast Screen (BDI-FS; log-

transformed); and the NEO Five-Factor Inventory (NEO-FFI)[14] (see Table 3). The Neuroticism scale (NEO-N) of the NEO-FFI reflects an individual's maladaptive stress response, NEO-N discriminates between major depressive disorder (MDD) and generalized anxiety disorder (GAD) in psychiatric samples,[15] and very high NEO-N has been proposed as a signature symptom of GAD.[15] Composite measures were calculated as the mean of NEO-N and MHI-A for anxiety, and the mean of BDI-FS and MHI-D for depression. Signs were transformed such that higher scores reflect worse anxiety or depression. As expected, the composite measures were highly correlated (r=0.700, p<0.001). These composite variables were used for all subsequent analyses. In the MEM CONNECT cohort, NEO-N score was used as a measure of anxiety and the Beck Depression Inventory-II (BDI-II) was used to measure depression. Characterization of anxiety and depression based on these measures is depicted in Table 3.

Measurement of disease burden.

T2 lesion volume (T2 LV) was quantified in patients who underwent 3D T1 and 3D T2 3.0T MR imaging (RADIEMS: Siemens Skyra, n=183; MEM CONNECT: GE Discovery, n=52). T2 LV was measured using a local thresholding segmentation technique (Jim 6.0, Xinapse System, www.xinapse.com); raw values were log-transformed.

Statistical analysis:

All variables with extreme values were winsorized (95% confidence interval). Associations of anxiety and depression to cognitive variables were evaluated using partial correlations controlling for age, sex, education, and IQ. Given known relationships of fatigue to depression and mood symptoms, an additional partial correlation was calculated with fatigue (measured as total score on the Fatigue Severity Scale[16]) entered as an additional covariate. In the RADIEMS sample, false discovery rate (FDR) correction was applied to all results to control for multiple comparisons. The same correction was not applied to the MEM CONNECT sample, as this analysis was driven by an *a priori* expectation of replication of the results found in the initial discovery sample.

Disease burden analysis:

Given the possibility that observed associations between mood symptoms and cognition may be mediated by disease burden (e.g., higher T2 lesion volume, as proposed by Ribbons et al[9]), we conducted an additional partial correlation entering T2 LV as a covariate to determine whether this changed our results.

RESULTS

Discovery cohort: In the RADIEMS cohort, lower anxiety was related to better nonverbal memory (r_p= −0.220, p=0.003) and lower depression was related to better attention/processing speed (r_p= −0.241, p=0.001). And, despite a strong relationship of fatigue to depression (r= 0.675, p=<0.001) and anxiety (r= −0.425, p=<0.001), controlling for fatigue in our analyses did not change results. *Replication cohort:* In the MEM CONNECT cohort, lower anxiety was related to better nonverbal memory (r_p= −0.271, p=0.028) and lower depression was related to better attention/processing speed (r_p= −0.367, p=0.002). In this

sample, there was a weak association of fatigue to depression (r= 0.244, p=0.049), and no association to anxiety (r= 0.124, p=0.321). As in the RADIEMS cohort, controlling for fatigue did not change any results. *Disease burden analysis:* When partial correlations were recalculated adding T2 LV as an additional covariate, results were unchanged. Table 4 summarizes results of all relationships of anxiety and depression to cognitive latent variables.

DISCUSSION

In two independent samples, anxiety and depression were associated with different cognitive functions: anxiety was related to nonverbal memory, and depression was related to attention and processing speed. This was consistent with our *a priori* hypothesis, informed by 1) our prior work showing a relationship of anxiety to memory function[17] and 2) recent studies reporting broadly consistent results.[8,9,11] Anxiety and depression present at much higher rates in MS than the general population,[1,4,18] and cognitive impairment affects approximately half of all persons with MS, yet interrelationships among these symptoms/comorbidities are not well understood. Our findings support links of different mood profiles (anxiety, depression) to specific, objectively measured cognitive functions (nonverbal memory, attention/processing speed) as opposed to simply linking general or overall worsening of mood to general or overall worsening of cognition. Anxiety and depression are related to increased self-reported cognitive impairment in MS,[19-21] likely perpetuating a widely held (and perhaps unhelpful) notion that mood issues are related to over-reporting of cognitive symptoms.[22] Our results bolster the accuracy of patient-reported cognitive changes that accompany mood symptoms, as they highlight the specificity of the relationship of mood issues to objective cognitive functioning. In addition, there is some degree of concordance between the clinical presentation of depression: anhedonia,[23] anergia,[24] diminished motivation, and reduced motor activity,[25] and its associated cognitive profile: decreased attention and slowed information processing speed. This finding provides evidence that aligns with the “cognitive effort hypothesis”: developed in the broader psychiatric literature to address observed relationships of depression to cognition,[26,27] this hypothesis proposes depression as related specifically to performance on tasks requiring effortful information processing, rather than those involving automatic processing. Anxiety, in contrast, typically not characterized by psychomotor slowing, was related in our study not to information processing speed, but to memory. Distinct cognitive signatures may reflect fundamental differences in the impact of mood symptoms/comorbidities on brain function, or may reflect differences in the impact of cognitive and/or brain changes on mood; these possibilities are not mutually exclusive. Given evidence for shared pathophysiological mechanisms underlying depression and anxiety from non-human animal models and psychiatric populations,[28-31] and clinical overlap in their presentation, cognition may represent a uniquely sensitive marker for understanding the functional correlates/consequences of neuropsychiatric symptoms.

To our knowledge, there are only three published studies in MS thus far to evaluate relationships of cognition to both anxiety and depression within the same sample.[8,9,11] The present study is novel and extends our knowledge for three key reasons: first, we show replication across two independent samples representing different disease stages (i.e., an

early cohort: 2.2 years from diagnosis; and a later cohort: 7.6 years from diagnosis). Second, in the present study we employ latent variables of cognition. Latent variables are superior to single test measures as they reflect the overlap of several tests and therefore represent more pure and stable variables of cognition. Additionally, the latent factor structure reveals to us the cognitive construct(s) measured by individual tests, as opposed to assigning individual tests an idea of what we think or want them to measure. Although latent variables have been widely embraced by cognitive neuroscience researchers in other clinical populations (notably, aging and Alzheimer's disease[32]), they have infrequently been adopted by MS researchers, which hinders advancement of our field and lends itself to inaccuracies in identifying the specific cognitive function(s) individual tests actually measure. The use of latent variables of cognition is essential as well for use in studies aiming to identify neural substrates of cognitive functions. Finally, none of the prior studies had access to lesion volume data, a noted limitation of several earlier studies.[33,34] Our inclusion of T2 LV as a proxy of disease burden allowed us to report that lesion volume was not responsible for specific relationships of anxiety and depression to cognitive function.

We now consider our findings in the context of the three prior studies conducted in MS. In a recent study conducted in a large (n=255) sample of MS patients, Whitehouse et al.[8] evaluated associations of depression and anxiety to performance on three tests: SDMT, California Verbal Learning Test (CVLT), and Letter-Number Sequencing (LNS). Anxiety was related to performance on all three tests, whereas depression was related only to SDMT performance. We note that the PCA we conducted in our derivation of latent variables revealed SDMT to load onto 3 of the 4 variables derived: language / verbal fluency and nonverbal memory in the MEM CONNECT cohort, and attention / speed in the RADIEMS cohort. This suggests that the single most useful (and most used) cognitive measure in the MS literature (often referred to not by its name, but simply as "processing speed") in fact measures several different cognitive functions, and/or different cognitive functions in different people. This bolsters the need to adopt latent variables of cognition in MS, as they are superior to less stable single test measures. In a well-designed study by Morrow and colleagues,[11] anxiety was related to performance on the Paced Auditory Serial Addition Test (PASAT) and BVMT-R immediate and delayed recall, whereas depression was associated with SDMT, BVMT-R delayed recall, and the Delis Kaplan Executive Function System Sorting Test (Descriptions score, but not Correct Sorts). Their sample (n=151) differed from ours in two key ways: first, they were further along in their disease course (average disease duration: 9.7±7.0 years), and second, they were much more homogeneous in racial/ethnic composition (97.4% Caucasian). The study by Ribbons et al.[9] found that for 322 patients with MS, after controlling for all clinical covariates, anxiety was the only mood factor that significantly predicted cognition, an association that was strongest for memory function.

Several key papers from the MS literature provide broader theoretical context for the findings of the present study. In a series of papers evaluating depression and cognition, Arnett and colleagues highlighted links of depression to speeded attentional capacity-demanding tasks[30] and tasks requiring controlled attention.[34] Importantly, the relationships were not explained by a number of carefully considered factors including age, disease variables, medications, premorbid intelligence, or primary visual or auditory deficits. In these seminal papers, the authors highlight the need for future work that (a) more precisely

parses out different components of cognitive functioning, and (b) includes MRI markers of disease burden, specifically T2 lesion volume (both of which are incorporated in the design of the present study). Additional recent work by Lubrini and colleagues[35] showing a link between depression and slowed information processing speed invoked the cognitive effort hypothesis (described above) to explain their findings.

Limitations of the current study include the cross-sectional design, which precludes interpretations regarding whether/how anxiety and depression predict trajectories of cognitive decline, and vice versa: whether cognitive changes may precede/cause mood changes. It is important to consider the possibility of distinct dynamic interrelationships of mood symptoms and cognition in MS, and not merely treat mood as a "confounder" in cognitive research. A strength of our study is that it will be extended in the future: both cohorts (MEM CONNECT and RADIEMS) are being followed longitudinally; thus, dynamic change in the mood-cognition relationships described herein will be evaluated at 3-year follow-up (currently being collected in the MEM CONNECT cohort, and to be collected starting in 2020 in the RADIEMS cohort). Whitehouse et al. noted that managing anxiety and depression symptoms may mitigate their effect on cognition[8]; likewise, we note that addressing cognitive issues may have a beneficial impact on mood symptoms. An additional limitation is that our evaluation of mood was limited to self-report questionnaires measuring current mood symptoms. Future work to more comprehensively evaluate neuropsychiatric symptoms in MS is warranted.

A recent consensus paper on cognition in MS highlighted the need to explicate shared neural bases for mood and cognitive dysfunction in order to advance development of effective cognitive treatments,[36] and this is consistent with seminal papers calling for future work to elucidate mechanisms underlying mood-cognition relationships in MS[33] (For a recent discussion of common underlying brain substrates of cognition and depression in MS, please see [37]).

Clarifying the impact of MS-specific neural changes (neuroinflammatory and neurodegenerative processes, demyelination, disconnection of critical brain regions, regional lesion volumes) as well as psychosocial influences including the lived experience of having a chronic, unpredictable disease on cognition, anxiety, and depression in persons with MS may ultimately guide the development of novel, targeted treatments for mood and cognitive issues. Moreover, consideration of mood symptoms may help identify different cognitive phenotypes with reasonable treatment targets (i.e., anxiety or depression). Cognition is very hard to treat, and we currently have no validated treatments. One reason for this is because cognition has historically treated as a unitary deficit (i.e., impaired versus non-impaired)[7] Identifying more precise cognitive phenotypes and considering interrelationships of cognition to mood has the potential to advance the field in our treatment approach for individuals with MS.

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Table 1.

Sample characteristics.

	RADIEMS (n=185)	MEM CONNECT (n=70)
Age (years)	34.4 ± 7.5	40.7 ± 11.1
Sex (% female)	123 (66.5%)	53 (77.1%)
IQ	108.3 ± 8.8	112.0 ± 10.0
MS Phenotype	165 RRMS, 20 CIS	70 RRMS
Years since diagnosis	2.2 ± 1.4	7.6 ± 6.9
EDSS (median, interquartile range)	1.0, 0-1.5	1.5, 0-1.0
T2 LV (milliliters; median, interquartile range)	1.5, 3.8	4.1, 7.4

IQ= estimated verbal intelligence quotient based on Wechsler Test of Adult Reading; RRMS= relapsing-remitting multiple sclerosis; CIS= clinically isolated syndrome; EDSS= Expanded Disability Severity Scale; T2 LV= T2 lesion volume.

Table 2.

PCA to derive latent variables of cognition in a) RADIEMS cohort and b) MEM CONNECT cohort.

RADIEMS (n=185)				
	Nonverbal Memory	**Language/ Verbal fluency**	**Verbal Memory**	**Attention / Speed**
Variables				
CANTAB PAL (TEA)	−.860			
CANTAB PAL (FAMS)	.850			
BVMT-R (DR)	.787			
BVMT-R (TL)	.763			
FAS		.792		
Digit Span		.718		
Animals		.655		
Stroop (color-word)		.601		.442
Stroop (color)		.584		.539
VPAL (DR)			.834	
VPAL (TL)			.813	
SRT (TL)			.791	
SRT (DR)			.784	
NIH PC				.751
SDMT				.471
MEM CONNECT (n=70)				
	Language / Verbal Fluency	**Verbal Memory**	**Attention / Speed**	**Nonverbal Memory**
Variables				
Stroop (color)	.886			
Stroop (word)	.872			
Stroop (color-word)	.769			
Animals	.703	.471	.430	
SDMT	.656			.476
FAS	.652		.566	
SRT (TL)		.900		
SRT (DR)		.875		
Digit span forward			.845	
Digit span back			.763	
Digit span sequencing	.502	.408	.734	
BVMT-R (DR)				.808
BVMT-R (TR)				.780

*Coefficients below .4 suppressed for display

CANTAB PAL= Cambridge Neuropsychological Test Automated Battery Paired Associates Learning, TEA= total errors adjusted, FAMS= first attempt memory score; BVMT-R= Brief Visuospatial Memory Test Revised, DR= delayed recall, TL= total learning; COWAT= Controlled Oral

Word Association Test, FAS= phonemic fluency condition, animals= semantic fluency condition; VPAL= verbal paired associates learning, DR= delayed recall, TL= total learning; SRT= Selective Reminding Test, DR= delayed recall, TL= total learning; NIH PC= NIH Pattern Comparison; SDMT= Symbol Digit Modalities Test (oral version).

Table 3.

Characterization of anxiety and depression in a) RADIEMS and b) MEM CONNECT cohorts.

RADIEMS (n=185)			
Anxiety (mean ± SD)		**Depression (mean ± SD)**	
MHI-A	63.0 ± 19.0	MHI-D	76.0 ± 17.3
NEO N	49.1 ± 11.4 *	BDI-FS	2.6 ± 2.7 (minimal)
MEM CONNECT (n=70)			
NEO N	51.4 ± 11.2 *	BDI-II	10.8 ± 8.3 (minimal)

* Neuroticism did not differ from normative mean (i.e., T=50; *p*'s=.314 and .291, respectively)

MHI-A: Mental Health Inventory, Anxiety subscale; MHI-D: Mental Health Inventory, Depression subscale; NEO N: NEO Five Factor Inventory, Neuroticism subscale; BDI-FS: Beck Depression Inventory, Fast Screen; BDI-II: Beck Depression Inventory-II.

Table 4.

Relationships of anxiety and depression to cognition in a) RADIEMS cohort and b)MEM CONNECT.

RADIEMS (n=185)		
	Anxiety	**Depression**
Nonverbal Memory	r_p= −.220, *p*=.003**	r_p= −.129, *p*=.086
Language Processing	r_p= −.012, *p*=.874	r_p= −.136, *p*=.070
Verbal Memory	r_p= .031, *p*=.677	r_p= .065, *p*=.390
Attention/Processing speed	r_p= −.146, *p*=.052	r_p= −.241, *p*=.001**
MEM CONNECT (n=70)		
Nonverbal Memory	r_p= −.271, *p*=.028*	r_p= −.237, *p*=.056
Language Processing	r_p= .076, *p*=.546	r_p= −.069, *p*=.582
Verbal Memory	r_p= −.041, *p*=.742	r_p= −.137, *p*=.272
Attention/Processing speed	r_p= −.221, *p*=.075	r_p= −.367, *p*=.002**

* *p*<.05,

** *p*<.01