

RELATIONSHIPS AMONG ANXIETY, DEPRESSION, AND EXECUTIVE FUNCTIONING IN MULTIPLE SCLEROSIS

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Anxiety is a common psychiatric symptom among patients with multiple sclerosis (MS), however compared to depression it is relatively under-studied. The relative contribution of anxiety and depression to cognitive functioning was evaluated among 77 persons with MS. Participants completed the Chicago Multiscale Depression Inventory, the State-Trait Anxiety Inventory, and neuropsychological measures of executive functioning. Regression analyses indicated that, although both depression and anxiety independently predicted performance on an index of executive functioning, anxiety was uniquely associated with cognitive functioning in MS, above and beyond depression. These results suggest that consideration of anxiety in the assessment and treatment of MS patients is warranted.

Keywords: Comorbidity; Autoimmune disorders of the nervous system; Neuropsychological tests; Affect; Thinking; Emotions.

INTRODUCTION

Depression and anxiety are among the most common psychiatric symptoms occurring in multiple sclerosis (MS). Several studies have observed a relationship between depression and executive functioning in MS (Arnett et al., 1999a, 1999b; Gilchrist & Creed, 1994), however the relationship between anxiety and executive functioning in MS remains unclear despite evidence in other populations documenting that anxiety has an important influence on tasks of executive function (Eysenck & Calvo, 1992). Anxiety is common in MS, with some studies citing higher rates of anxiety than depression (Feinstein, 1999). Prevalence rates of clinically significant symptoms of anxiety vary from 12% to 90%, depending on cohort characteristics and assessment methodology; however most studies indicate prevalence rates ranging from 30% to 53% (Beiske et al., 2008; Bruce & Arnett, 2008; Dalos, Rabins, Brooks, & O'Donnell, 1983; Diaz-Olavarrieta, Cummings,

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Velazquez, & Garcia de la Cadena, 1999; Feinstein, 1999; Janssens et al., 2006; Korostil & Feinstein, 2007; Zorzon et al., 2001). Epidemiological evidence in MS also suggests that anxiety often co-occurs with depressive symptoms (Arias Bal et al., 1991; Colombo, Armani, Ferruzza, & Zuliani, 1988; Feinstein, 1999; Zorzon et al., 2001). The co-morbidity of anxiety and depression is associated with a number of poor outcomes including: greater social dysfunction, greater psychological distress, and increased suicidal ideation, thereby adding to the overall distress and disability of MS patients (Feinstein, 1999).

Few studies have evaluated the relationship between anxiety and cognitive functioning in MS. Using a cognitive composite index comprised of verbal learning and executive functioning measures, Simioni and colleagues (Simioni, Ruffieux, Bruggimann, Annoni, & Schlupe, 2007) found that 63% of patients who met criteria for cognitive impairment had increased anxiety scores, as compared to 41% of patients classified as cognitively intact. Using a larger battery of neuropsychological measures, Stenager and colleagues (Stenager, Knudsen, & Jensen, 1994) found that only a measure of executive functioning (Trail Making Test – Part B) was significantly associated with anxiety as measured by the State-Trait Anxiety Inventory (STAI). Importantly, this relationship held even when the authors used the ratio of Trails A to Trails B to control for potential motor speed deficits in the MS patients.

Most studies evaluating relationships among psychiatric symptoms and cognitive functioning in MS have focused on the role of depression (Arnett, Higginson, & Randolph, 2001; Thornton & Raz, 1997). Using Baddeley's model of working memory as a conceptual framework for one component of executive functions (Baddeley, 1986; Baddeley & Hitch, 1974; Engle & Oransky, 1999), Arnett and colleagues observed that depression appeared to be associated with measures that draw on resources of the Central Executive System. Specifically, depressed MS patients demonstrated poorer performance on a task of working memory that placed demands on both processing and storage functions (i.e., a reading span task) as compared with a task with solely storage demands (i.e., a word span task) (Arnett et al., 1999a, 1999b). Although decreases in working memory have been noted in MS patients regardless of their depression status, this study suggested that depression might have an important impact on an important component of executive functioning in MS.

In sum, although both depression and anxiety are common among persons with MS, depression has received the bulk of attention from researchers in the field. Several studies have demonstrated a relationship between depression and executive dysfunction in MS. The specific relationship between anxiety and executive functioning in MS remains unclear. To our knowledge there are no published studies examining the influence of both anxiety and depression on any aspect of cognitive functioning in MS. The purpose of this investigation was to determine the independent effects of anxiety and depression on specific domains of executive functioning. As our index of executive functioning, we used measures previously studied in the context of depression (Arnett et al., 2001). We hypothesize first that anxiety will be associated with executive functioning, and second that anxiety will predict executive functioning independent of depression.

METHOD

Participants

Participants included MS patients recruited from neurologists and a local MS society in the northwestern United States. Participants were excluded if they had a history of alcohol or drug abuse, any nervous system disorder other than MS, severe motor or visual impairment that could interfere with cognitive testing, pre-morbid history of learning disability, or substantial difficulty being evaluated at one of the testing centers (either because of limiting physical or neurological impairment or because of not living within a convenient distance to a testing center). After these subsequent exclusions, the MS group utilized in data analyses consisted of 77 participants (only a subset of 63 participants were administered the Tower of London Task). Human data included in this manuscript were obtained in compliance with regulations of our institution's human protections program.

Each MS participant was diagnosed with definite or probable MS by a board-certified neurologist using established criteria (Poser et al., 1983). The neurologist also determined disease course on the basis of published criteria (Lublin & Reingold, 1996). Duration of illness from symptom onset and diagnosis, and neurological disability (Expanded Disability Status Scale, EDSS; Kurtzke, 1983) were also rated using a validated patient self-report methodology. The EDSS was converted into a questionnaire form in consultation with a board-certified neurologist, and patients rated themselves on this EDSS questionnaire within 1 week prior to testing. The EDSS was subsequently rated by an experienced neuropsychologist with expertise in MS (PA) after he received instruction from a neurologist specializing in MS. It has been more typical in this literature to use clinically based assessments of MS related disability. However, supporting this approach, Solari et al. (1993) found that the intraclass correlation between a patient self-administered version of the EDSS and neurologists' independent ratings was high ($r = .84$). Further information on recruitment and evaluations are described in detail in by Arnett and colleagues (1999a).

Depression and anxiety measures

Chicago Multiscale Depression Inventory (CMDI). The CMDI (Nyenhuis et al., 1998) was developed specifically for the purpose of assessing depressive symptoms in MS and other medical/neurological patient groups. This is a 42-item Likert-type self-report scale with item choices ranging from 1 (not at all) to 5 (extremely). This theoretically and empirically derived measure allows for the differentiation among various aspects of depression including mood, evaluative, and vegetative components. Due to the potential confounds of including vegetative symptoms when evaluating depression in MS, we utilized only a composite of the evaluative and mood subscales of the CMDI as a measure of core characteristics of depression. Similar approaches have been suggested by Nyenhuis et al. (1998), and have been utilized within previous studies on depression and cognitive functioning in MS (Arnett et al., 1999a, 1999b, 2001).

State-Trait Anxiety Inventory (STAI). We used the STAI (Spielberger, 1983) to assess symptoms of anxiety. This measure has been used extensively in research and clinical practice, and consists of 40 Likert-type items, with responses ranging from 1 (almost never) to 4 (almost always). A total of 20 items are each allocated to assess State and Trait anxiety indices.

Neuropsychological measures

Neuropsychological measures were administered in a consistent order by a trained examiner. Order of measures was reversed for approximately half of the patients (see Table 1 later).

Shipley Vocabulary Test. The Vocabulary subtest of the Shipley Institute of Living Scale (Zachary, 1991) was utilized as an estimate of pre-morbid intellectual functioning. Participants are administered 40 vocabulary words and must choose a word from four possible choices that is most similar in meaning to the stimulus word.

Visual Elevator Subtest of the Test of Everyday Attention (TEA). The Visual Elevator Subtest of the TEA (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994) is considered a measure of attentional switching, or cognitive flexibility. It is a timed task in which participants must determine the floor on which a visually presented elevator is located. The elevator begins on the first floor and moves one floor each time it is presented. Arrows are presented occasionally and are used to indicate direction change. The test consists of 10 trials on which all floors and arrows are presented on a single page for each trial. Time per switch for correct items, the index that captures both speed and switching components of the task, was used as the dependent variable.

Paced Auditory Serial Addition Test (PASAT). This task (Gronwall, 1997; Gronwall & Wrightson, 1974) requires participants to add pairs of numbers serially, while suppressing their successive additions of numbers. In the version used in the proposed study (Rao, Leo, Haughton, St Aubin-Faubert, & Bernardin, 1989) there are two strings of single-digit numbers, one presented every 3 seconds, and another presented every 2 seconds. Number of correct additions out of 60 possible for each task is the primary scoring index. Because of the high correlations between the two strings in previous MS investigations ($r = .89$, $p < .0001$; Higginson, Arnett, & Voss, 2000), the total correct for each task was summed to create a single index.

Symbol Digit Modalities Test (SDMT). In order to minimize possible confounding effects of slow motor writing speed characteristic of MS, the oral version of the SDMT (Smith, 1982) was used. It is a speeded task that involves the conversion and coding of geometric designs into oral number responses. Total correct in 90 seconds was used as the dependent variable.

Reading Span Task. This task (Arnett, et al., 1999a) consists of a primary task and a background task and was designed to assess the central executive component of working memory. The first component is a background task that requires participants to read aloud a sentence presented in a booklet. The primary

Table 1 Patient characteristics, disease characteristics, and neuropsychological performance scores

	<i>M</i>	<i>SD</i>
Age	46.58	8.20
Education (years)	14.86	2.36
Diagnosis duration (years)	7.31	6.06
Symptoms duration (years)	14.53	10.00
Disability (EDSS ^a)	4.65	1.47
Sex, <i>n</i> (%)		
Male	16 (21%)	
Female	61 (79%)	
CMDI – Mood + Evaluative ^b	41.66	15.61
STAI – State ^c	36.91	10.36
STAI – Trait ^d	38.78	9.72
Estimated intellectual functioning ^e	54.55	6.74
PASAT ^f	86.89	24.58
SDMT-Oral ^g	51.51	11.02
TEA Visual Elevator ^h	4.37	1.35
Reading Span Test ⁱ	26.50	11.05
Test order		
A	40 (52.6%)	
B	36 (47.4%)	
Diagnostic category		
Clinically Definite, <i>n</i> (%)	69 (89.6%)	
Laboratory Definite, <i>n</i> (%)	4 (5.2%)	
Clinically Probable, <i>n</i> (%)	3 (3.9%)	
Laboratory Probable, <i>n</i> (%)	1 (1.3%)	
Clinical course		
Relapsing-Remitting, <i>n</i> (%)	48 (62.3%)	
Primary-Progressive, <i>n</i> (%)	7 (9.1%)	
Secondary-Progressive, <i>n</i> (%)	20 (26.0%)	
Progressive-Relapsing, <i>n</i> (%)	2 (2.6%)	

^aKurtzke's Expanded Disability Status Scale. ^bCMDI – Mood + Evaluative = Chicago Multiscale Depression Inventory – Mood and Evaluative scale combined. ^cSTAI – State = State-Trait Anxiety Inventory – State scale. ^dSTAI – Trait = State-Trait Anxiety Inventory – Trait Scale. ^eShibley Institute of Living Scale – Vocabulary Subtest T-score. ^fPASAT = Paced Auditory Serial Attention Test – Sum of 2 second and 3 second trials combined. ^gSDMT = Symbol Digit Modalities Test. ^hTEA = Test of Everyday Attention, average time per correct switch. ⁱReading Span Test – words correctly recalled. Values for the CMDI and STAI variables are raw scores.

task requires the participant to keep track of and recall single, one-syllable words that are presented after participants have read each sentence. When participants come to a blank card, they are instructed to try and recall all end words since the previous blank card. The task order consists of 3 two-sentence trials, 3 three-sentence trials, moving up in one-sentence increments until a maximum of 3 six-sentence trials is reached. The task was discontinued if the participant was unable to correctly recall all of the words of one trial within a sequence of two consecutive blocks. The dependent variable was total number of words correctly recalled.

Summary index of cognitive functioning

An exploratory principal components factor analysis with varimax rotation revealed a single factor that we entitled “executive functioning.” Factor loadings for the executive functioning index were acceptable and ranged from .50 (for the Reading Span Task) to $-.89$ (for the Visual Elevator subtest). A summary index was created by using the factor score derived from this factor analysis.

RESULTS

Patient and disease characteristics

Participant characteristics of the sample and neuropsychological performance scores are depicted in Table 1. Analyses of Variance (ANOVAs) were performed comparing performance on the executive functioning index across disease course types. Because there were only two Progressive-Relapsing patients, they were excluded from the disease course analyses, and this ANOVA was not statistically significant. Correlations were also conducted between participant characteristics and the executive functioning index. The following variables were significantly correlated with the executive functioning index: EDSS, $r(77) = -.37$, $p < .005$; Shipley Vocabulary t -score, $r(77) = -.23$, $p < .05$; and diagnosis duration, $r(77) = -.32$, $p < .01$. These patient and disease characteristics were controlled for in the subsequent regression analyses.

Associations between anxiety, depression, and executive functioning

Correlations were conducted in order to determine the zero-order relationships among symptoms of depression, anxiety, and the executive function index. As shown in Table 2, all correlations between the anxiety and the executive functioning index were significant, supporting our first hypothesis that anxiety would be associated with executive functioning. The depression index, the STAI-State scale, and the STAI-Trait scale were also significantly correlated with the executive function index (Table 2).

In order to address hypothesis 2, two separate hierarchical regression analyses were conducted to assess whether state and/or trait anxiety contributed unique

Table 2 Correlations of depression and anxiety scales with executive functioning

	CMDI Mood + Evaluative ^a ($n = 77$)	STAI ^b State Anxiety ($n = 77$)	STAI Trait Anxiety ($n = 77$)	Executive Functioning Index ($n = 77$)
STAI State Anxiety	0.50**	1.00		
STAI Trait Anxiety	0.61**	0.70**	1.00	
Executive Functioning Index	-0.45**	-0.38**	-0.27*	1.00

^aCMDI Mood + Evaluative = Chicago Multiscale Depression Inventory, Mood and Evaluative Subscales combined. ^bSTAI = State-Trait Anxiety Inventory. * $p < .05$. ** $p < .01$.

Table 3 Hierarchical regression analyses for Chicago Multiscale Depression Inventory and State-Trait Anxiety Inventory indices predicting executive functioning

Variable	R^2	adj R^2	ΔR^2	ΔF	Δp -level
Patient and disease characteristics ^a	0.18	0.15	0.18	5.40	<0.01
Depression: CMDI Mood + Evaluative ^b	0.29	0.25	0.11	11.60	<0.01
Anxiety STAI State ^c	0.35	0.28	0.04	4.53	<0.05
Patient and disease characteristics ^a	0.18	0.15	0.18	5.40	<0.01
Depression: CMDI Mood + Evaluative ^b	0.29	0.25	0.11	11.60	<0.01
Anxiety STAI Trait ^d	0.29	0.24	0.00	0.14	0.72

^aPatient and disease characteristics include Shipley Vocabulary T-score, Expanded Disability Status Scale, and disease duration. ^bCMDI Mood + Evaluative = Chicago Multiscale Depression Inventory, Mood and Evaluative Subscales combined. ^cSTAI State = State-Trait Anxiety Inventory, State Scale. ^dSTAI Trait = State-Trait Anxiety Inventory, Trait Scale.

variance to the executive functioning index after accounting for depression (see Table 3). After entering significant patient and disease factors, the depression score was entered and accounted for 11% of the variance in executive functioning, $F(1, 70) = 11.6$, $p < .01$. State anxiety was then subsequently entered and contributed another 4% unique variance, $F(1, 68) = 4.53$, $p < .05$. In a separate regression, Trait anxiety did not contribute significantly to the equation.

DISCUSSION

The purpose of this study was to evaluate the effect of anxiety, independently of depression, on neuropsychological test performance in a cohort of well-defined patients with MS. The first hypothesis, that higher levels of anxiety would be associated with decreased cognitive performance, was generally supported. Correlational analyses suggested that both increased State and Trait anxiety were associated with decreased performance on a composite index of executive functioning. Although anxiety and depression frequently co-occur, they represent distinct forms of psychopathology, which may differentially impact executive functioning. As such, another important goal of this investigation was to evaluate the extent to which anxiety and depression were associated with the same or unique aspects of variance in our index of executive functioning. Our second hypothesis stated that anxiety and depression would be independently associated with executive functioning. This hypothesis was partially supported. We found that State, but not Trait, anxiety predicted performance on the index of executive functioning above and beyond that which could be explained by depression.

These findings are consistent with two prior studies demonstrating a relationship between anxiety and tasks of executive function in MS (Stenager et al., 1994). In an extension of previous work showing the relationships among depression and executive functioning (Arnett et al., 1999a, 1999b, 2001), this study is unique and the first to show that high (State) anxiety also predicts decreased executive functioning independently of depression.

These findings are also consistent with the processing efficiency theory of anxiety and cognitive functioning posited by Eysenck and Calvo (1992). In this theory a component of State anxiety, anxious apprehension or worry, is considered to be a verbally mediated subvocal preoccupying cognition that has been hypothesized to occupy some of the capacity of the central executive system and the articulatory loop components of working memory (Ikeda, Iwanaga, & Seiwa, 1996). Slowed response speed is an indication of the extra effort, or processing resources, allocated to the task. In the present study, State-anxious MS patients demonstrated poorer processing efficiency on executive tasks, in particular executive tasks that include a speeded component. The finding that State, but not Trait anxiety places demands on processing resources is also consistent with the theoretical conceptualization of State anxiety as specific actions or active processing that take place at a given period of time and place (Spielberger, 1983). In contrast, Trait anxiety is less likely to place demands on the central executive system, as it is generally conceptualized as a relatively stable construct that may be more associated with a personality structure or disposition.

Because of the cross-sectional and correlational nature of our design it was not possible to make conclusive causal statements regarding our data. Thus, although our data are consistent with the notion that State anxiety impedes executive functioning in MS, it is also plausible that the causal direction is reversed, or that some third variable underlies the relationship observed. The assumption that many deficits noted in MS patients chiefly result from primary factors (i.e., lesions, CNS involvement) is not entirely satisfactory. An implication of the present study is that anxiety may also be a source of cognitive compromise in MS patients.

There are also other limitations to our study. There may be some limitations regarding the generalizability of our data. The ratio of MS in women to men is typically about 2:1, whereas in this study the ratio was closer to 4:1. The higher frequency of depression and anxiety among women in the general population may have resulted in an increased prevalence of psychiatric distress (i.e., anxiety) in this MS sample. A third limitation is that anxiety and depression were assessed only by means of self-report. A "multi-vantage" assessment of anxiety and depression may provide a useful means by which to further assess psychopathology in MS patients. Also, only the mood and negative evaluative scales of the CMDI were utilized in order to limit potential confounds of neurovegetative symptoms of depression that may overlap with the neurological symptoms of MS (Beeney & Arnett, in press). Although this is a conservative approach to the assessment of depression in MS, it may not be comprehensive (Randolph, Arnett, Higginson, & Voss, 2000). Regarding our measurement of anxiety, although the STAI is highly reliable and valid, it does not provide detailed information regarding aspects of anxiety that may be important to assess in MS patients in relation to cognitive performance, namely anxious apprehension or worry. Although anxiety and depression represent distinct psychological phenomena, there is some symptom overlap, potentially creating problems of multicollinearity. Our measures were correlated; the correlation between our depression index and State anxiety was .50 and with Trait anxiety the correlation was .61. Thus, although our depression and anxiety indices shared variance, these constructs certainly fall short of complete overlap. A final limitation to our study was the absence of a non-MS control group. As such, it was not

possible to evaluate whether the associations we observed were specific to MS patients or to an anxious population in general.

Overall, our study highlights the importance of assessing and treating psychiatric co-morbidities. Regarding assessment, consideration of anxiety in addition to depression appears to be warranted. The treatment of anxiety may benefit patients with MS not only by alleviating psychiatric distress, but also by increasing the availability of cognitive resources.

Future research should include a systematic evaluation of the development and course of anxious and depressive symptoms over time and their relationship to cognitive functioning in MS. Also, the addition of neuroimaging data will prove valuable for examining the relative contribution of primary (i.e., MS lesions, structural brain changes) disease processes on both psychiatric and cognitive functions. Future research could also involve the treatment of depression and anxiety in MS patients so that the impact of such treatment on cognitive functioning could be evaluated. With augmented empirical knowledge of these relationships, the targeted identification and treatment of psychiatric disorders among MS patients can be improved.

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