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Anxiety and depression affect performance on the symbol digit modalities test over time in MS and other immune disorders

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Abstract

Background: Longitudinal studies assessing depression and anxiety effects on cognition in multiple sclerosis (MS) are limited.

Objective: We tested whether within-person fluctuations in symptoms of depression or anxiety over time affect cognition in persons with MS, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and a lifetime history of depression/anxiety disorders (DEP/ANX) but without an immune-mediated inflammatory diseases (IMID).

Methods: We followed participants (MS: 255, IBD: 247, RA: 154, and DEP/ANX: 306) for 3 years. Annually, they completed the hospital anxiety and depression scale (HADS) and cognitive tests including the symbol digit modalities test (SDMT). We evaluated associations of elevated symptoms (scores $\geqslant 11$) of anxiety (HADS-A) and depression (HADS-D) with SDMT z-scores using multivariable linear models—estimating between-person and within-person effects.

Results: Participants with MS performed worse on the SDMT than participants in the DEP/ANX cohort ($\beta = -0.68$; 95% CI: -0.88, -0.48). Participants with elevated HADS-A scores performed worse on the SDMT than those without elevated scores ($\beta = -0.43$; 95% CI: -0.65, -0.21), particularly those with RA. Time-varying within-person elevations in depressive symptoms were associated with worse SDMT performance ($\beta = -0.12$; 95% CI: -0.21, -0.021).

Conclusions: Across persons, elevated symptoms of anxiety adversely affected information processing. Elevated symptoms of depression within-persons over time were associated with declines in information processing speed.

Keywords: Multiple sclerosis, cognition, depression, anxiety, symbol digit modalities test

Introduction

Cognitive impairment affects 40%–70% of individuals with multiple sclerosis (MS), adversely affecting work and social roles.[1] The characteristics and course of cognitive impairment in MS are heterogeneous, potentially due to comorbidity in part. Cross-sectional studies suggest that depression and anxiety are associated with lower cognitive function in MS.[2,3] Previously, we found that symptoms of depression and anxiety were associated with lower cognitive function (processing speed, verbal learning, and working memory) in MS and in other immune-mediated inflammatory diseases (IMID: inflammatory bowel disease (IBD) and rheumatoid arthritis (RA)).[4] Although MS is a central nervous system (CNS) disease, while IBD and RA are not, symptoms of depression and anxiety affected cognitive function similarly in MS, IBD, and RA and persons with lifetime depression or anxiety (DEP/ANX) but no IMID.[4]

Most studies examining associations between psychiatric comorbidity and cognition in MS have been

cross-sectional[2,4–6] and longitudinal studies assessing depression and anxiety effects on cognition are limited.[7,8] It is unknown whether the effects of psychiatric comorbidity on cognition over time in MS differ from those in other IMID or in persons with DEP/ANX but no IMID. Comparisons across these populations can help disentangle the relationships between inflammation, direct CNS involvement, and symptoms of depression and anxiety, on cognition. Because psychiatric comorbidities are potentially modifiable, these are important knowledge gaps. Therefore, we extended our prior work[4] to evaluate the association between psychiatric comorbidity and changes in cognitive function over time in individuals with MS, IBD, RA, and DEP/ANX but no IMID. We hypothesized that within-person fluctuations in symptoms of depression or anxiety would be associated with changes in cognitive function.

Methods

Study populations
We conducted this study in Manitoba, Canada. As described previously, we enrolled four cohorts of participants in a longitudinal study assessing the effects of comorbid depression and anxiety disorders in IMID.[9] These cohorts included individuals with definite MS, IBD (Crohn's disease or ulcerative colitis), and RA. Also included was a cohort with a lifetime history of a diagnosis of depression or an anxiety disorder or both, without any IMID; current depression or anxiety disorder was not required for enrollment. From November 2014 to June 2016, participants were recruited using multiple strategies.[9] All were aged ≥18 years and provided informed consent. The study was approved by the University of Manitoba Health Research Ethics Board.

Participants completed questionnaires and cognitive tests at enrollment and at three annual follow-up visits.[9] A semi-structured psychiatric interview, the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision* (*DSM*-IV-TR) axis I disorders—Research Version (SCID) was also completed at the first study visit.[10] This identified current and lifetime diagnoses of depression and anxiety disorders at enrollment.

Psychiatric morbidity
Participants reported symptoms of depression and anxiety using the hospital anxiety and depression scale (HADS),[11] which is validated for medical patients and for use in MS, IBD, and RA populations.[12–14] The HADS includes 14 items that assess symptoms of depression (HADS-D) and anxiety (HADS-A); total scores on each scale range from 0 to 21. At each visit, we classified participants as to whether they had clinically meaningful symptoms of depression (HADS-D score) or anxiety (HADS-A score). The literature varies regarding the optimal cut-point for the HADS in MS,[12,15] IBD, and RA. Therefore, we employed the more specific cut-point of ≥11, which indicates clinically meaningful symptoms of depression and anxiety.[11]

Cognitive function
Based on the cognitive domains often affected in individuals with MS, IBD, RA, and DEP/ANX,[16,17] we assessed cognitive function using the oral version of the Symbol Digit Modalities Test (SDMT),[18] the California Verbal Learning Test-second edition (CVLT-II),[19] and the letter number sequencing subtest (LNS) from the Wechsler Memory Scale-third edition.[20] The SDMT assesses processing speed, the CVLT-II assesses verbal learning and memory, and the LNS assesses working memory. To reduce practice effects, we used alternate forms of the SDMT and CVLT-II at the second and fourth visits. We used Canadian regression-based norms to convert raw scores for the SDMT and CVLT-II, including verbal learning (trials 1–5) and delayed recall memory (long-delay free recall trial) to age-, sex-, and education-adjusted *z*-scores.[21,22] For the LNS test, regression-based norms were not available so we used age-adjusted *z*-scores.[20] We classified participants as impaired on each test if their *z*-score fell at −1.5 or lower.[23] We estimated premorbid intelligence using the Wechsler test for adult reading.[24]

Covariates
Fixed covariates included age at symptom onset (continuous) and disease group (MS, IBD, RA, and DEP/ANX (reference group)). We did not include current age, gender, or education as these covariates were captured in cognitive *z*-scores, save for the LNS *z*-score. Time-varying covariates included body mass index (BMI, continuous), smoking (past, current, and never (reference group)), and vascular comorbidities, given their potential influence on the outcomes of interest.[25] We calculated BMI based on measured height and weight. Participants reported comorbidities using a validated questionnaire,[26] based on which we classified participants as hypertensive (yes vs. no), diabetic (yes vs. no), or hyperlipidemic (yes vs. no).

Analysis
We included participants who had completed ≥1 visit. The primary outcome was processing speed as

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measured by the SDMT. Secondary outcomes included verbal learning, delayed recall memory, and working memory.

To determine the effect of psychiatric comorbidity on cognitive function, we used generalized linear models with an identity link and generalized estimating equations with an unstructured working correlation to account for dependence of observations within individuals. These models produce population averages of within-person and between-person effects, but can be parameterized to distinguish between these effects using separate variables.[27] A priori, the independent variables of interest were within-person changes in the presence or absence of clinically meaningful symptoms of depression and anxiety, as defined above. We constructed separate multivariable models for four cognitive *z*-scores: (1) SDMT, (2) CVLT-II verbal learning, (3) CVLT-II delayed recall, and (4) LNS. For the LNS model, we added gender and years of education (continuous) as these did not contribute to the *z*-scores. We included covariates as described above. We tested for interactions between disease group and the psychiatric comorbidity variables only in the presence of a main effect of psychiatric comorbidity. We also tested for interactions between (1) the within-person changes in depression and anxiety symptoms and (2) the between-person changes in depression and anxiety symptoms. We considered a *p* value ⩽ 0.05 statistically significant for the primary outcome. For secondary outcomes, we applied a Benjamini–Hochberg correction for multiple comparisons, with a false discovery rate of 0.10.

Statistical analyses were conducted using SAS V9.4 (SAS Institute, Inc., Cary, NC).

Results
We enrolled 255 participants with MS, 247 with IBD, 154 with RA, and 306 with DEP/ANX.[4] Of the 962 participants, 833 (86.6%) completed four visits; 21 participants died before study completion (MS: 8, IBD: 7, RA: 3, and DEP/ANX: 3). Participants who did not complete follow-up were more likely to be non-white, smokers, to have elevated symptoms of depression or anxiety, and to have lower cognitive performance (Supplemental Table e1). Most participants were women and white; mean (SD) age was 49.2 (14.2) years. Participants with RA were older than participants in other groups; the IBD group had the lowest proportion of women (Table 1). No new between-group differences in demographic characteristics developed by the final visit (Supplemental Table e2).

Mean HADS scores are shown in Supplemental Figure e1. The proportion of participants with elevated symptoms of depression was highest in the lifetime DEP/ANX group at all visits (Table 1, Figure 1(a)). This proportion rose slightly over the study period in the MS group and fluctuated in the other two groups (Figure 1(a)). Overall 171 participants (MS: 45, IBD: 19, RA: 19, and DEP/ANX: 88) were shifted between elevated and non-elevated depressive symptoms during the study. The proportion of participants with elevated symptoms of anxiety was also highest in the DEP/ANX group at all visits. The proportion of participants with elevated symptoms of anxiety was more stable over time in all groups than those observed for elevated symptoms of depression (Figure 1(b)). Overall 275 (MS: 62, IBD: 41, RA: 35, and DEP/ANX: 137) participants were shifted between elevated and non-elevated anxiety symptoms during the study; of these, 90 participants (MS: 22, IBD: 8, RA: 13, and DEP/ANX: 47) were also shifted between elevated and non-elevated depressive symptoms.

At enrollment, participants with MS had lower *z*-scores with respect to processing speed, verbal learning, and delayed recall memory than the other groups (Table 1). Participants with MS were more likely to demonstrate impaired processing speed, verbal learning, and delayed recall memory at all visits (Figure 2 and Supplemental Figure e2).

Multivariable analysis
Primary outcome. On multivariable analysis, participants with MS had worse performance on the SDMT than participants in the DEP/ANX group (β = −0.68; 95% CI: −0.88, −0.48).

On average, at any given point in time (between-effects), participants with HADS-A scores ⩾ 11 demonstrated worse performance on the SDMT than those with HADS-A scores < 11, but participants with elevated HADS-D scores did not (Table 2). In contrast, time-varying within-person differences in anxiety were not associated with changes in SDMT scores, but elevated symptoms of depression were associated with worse performance. We observed an interaction between cohorts with the magnitude of the between-person effects of anxiety being greater in the RA cohort than all other cohorts (Table 2). We did not observe any statistically significant interactions between the within-person changes in depression and anxiety symptoms or the between-person changes in depression and anxiety symptoms.

Table 1. Participant characteristics at enrollment.

Covariate	MS (N=255)	IBD (N=247)	RA (N=154)	DEP/ANX (N=306)	p value
Women, n (%)	208 (81.6)	156 (63.2)	131 (85.1)	234 (76.5)	<0.001
White, n (%)	217 (85.4)	210 (85.4)	116 (75.3)	245 (80.1)	0.025
Age (years), mean (SD)	51.1 (12.9)	47.4 (14.8)	59.5 (11.7)	43.9 (12.9)	<0.001
Diabetes, n (%)	20 (7.8)	10 (4.1)	12 (7.8)	23 (7.5)	0.27
Hypertension, n (%)	57 (22.4)	45 (18.2)	55 (35.7)	62 (20.3)	<0.001
Hyperlipidemia, n (%)	46 (18.0)	31 (12.6)	38 (24.7)	54 (17.7)	0.021
Current smoker, n (%)	57 (22.4)	42 (17.0)	22 (14.3)	64 (20.9)	0.15
BMI, mean (SD)[a]	28.9 (7.3)	27.5 (6.2)	28.8 (6.7)	29.9 (7.9)	0.0032
Diagnoses of depression/anxiety disorders[b]					
Lifetime MDD, n (%)	105 (41.3)	98 (39.7)	58 (37.9)	251 (82.0)	<0.0001
Current MDD, n (%)	26 (10.2)	21 (8.5)	17 (11.1)	85 (8.9)	<0.0001
Lifetime anxiety disorder, n (%)	58 (22.8)	61 (24.7)	44 (28.8)	211 (69.0)	<0.0001
Current anxiety disorder, n (%)	35 (13.8)	47 (19.0)	33 (21.6)	169 (55.2)	<0.0001
Symptoms of depression/anxiety					
HADS-D $\geq$ 11, n (%)[c]	20 (7.91)	16 (6.48)	15 (9.74)	81 (26.5)	<0.001
HADS-A $\geq$ 11, n (%)[d]	40 (15.8)	41 (16.7)	21 (13.7)	188 (61.4)	<0.001
HADS-D, mean (SD)[c]	4.9 (3.7)	3.9 (3.7)	4.9 (3.8)	8.2 (4.3)	<0.001
HADS-A, mean (SD)[d]	5.9 (4.2)	6.3 (4.1)	6.7 (3.9)	11.4 (4.0)	<0.001
Cognitive function z-scores					
FSIQ estimate, mean (SD)	106.6 (9.0)	109.5 (8.5)	105.7 (9.7)	108.2 (9.0)	0.0002
SDMT, mean (SD)	−0.7 (1.1)	0.08 (1.1)	0 (0.97)	−0.2 (1.2)	<0.001
CVLT verbal learning, mean (SD)	−0.52 (1.6)	−0.35 (1.4)	−0.06 (1.3)	−0.29 (1.5)	0.017
CVLT delayed recall, mean (SD)	−0.62 (1.5)	−0.45 (1.3)	−0.25 (1.3)	−0.24 (1.3)	0.003
LNS, mean (SD)	−0.13 (0.93)	0.21 (0.9)	−0.31 (0.82)	0.15 (0.93)	<0.001

MS: multiple sclerosis; IBD: inflammatory bowel disease; RA: rheumatoid arthritis; DEP/ANX: depressed or anxious without an immune-mediated inflammatory disease; BMI: body mass index; SD: standard deviation; MDD: major depression disorder; HADS: hospital anxiety and depression scale; FSIQ: full scale intelligence quotient estimated from the Wechsler test of adult reading; SDMT: symbol digit modalities test; CVLT: California verbal learning test; LNS: letter number sequencing test.
[a]Seven missing for MS, one missing for RA, and three missing for DEP/ANX.
[b]Anxiety disorder includes generalized anxiety disorder, panic disorder, social phobia, agoraphobia, and special phobias; one missing for MS and one missing for RA.
[c]Two missing for MS.
[d]One missing for MS, one missing for IBD, and one missing for RA.

Secondary outcomes. On multivariable analysis, participants with MS had worse performance than participants in the DEP/ANX group with respect to verbal memory (β=−0.33; 95% CI: −0.58, −0.086), delayed recall memory (β=−0.36; 95% CI: −0.58, −0.13), and working memory (β=−0.27; 95% CI: −0.42, −0.12). Participants with RA also had worse working memory than participants with DEP/ANX (β=−0.44; 95% CI: −0.60, −0.28).

With respect to verbal memory, participants with HADS-A scores $\geq$ 11 had lower performance than participants with HADS-A scores < 11, but this was not statistically significant after accounting for the false discovery rate. Participants with elevated HADS-D scores did differ with respect to verbal memory from participants who did not have elevated scores. Time-varying within-person differences in depression and anxiety were not associated with changes in verbal learning. Elevated symptoms of depression and anxiety were not associated with delayed recall memory either between or within-persons. Participants with elevated symptoms of anxiety had lower working memory than participants without elevated symptoms of anxiety, but this finding was not statistically significant after accounting for the false discovery rate.

Discussion
We evaluated the association between psychiatric comorbidity and changes in cognitive function among

cohorts with MS, IBD, RA, and a cohort with a history of depression or anxiety but no IMID. Symptoms of depression and anxiety fluctuated, likely reflecting factors such as incident depressive or anxiety disorders and remission of existing disorders. At any given point in time, elevated symptoms of anxiety were

associated with slower processing speed (~5 points on the SDMT) and lower verbal learning in all cohorts studied, including in the MS cohort. The magnitude of the effect of elevated anxiety symptoms was greatest in the RA cohort. We also found that the development of elevated symptoms of depression within-persons over time was associated with slower processing speed across all cohorts, amounting to a difference of 1.6 points on the SDMT.

In those with MS and the other cohorts studied, the proportion of individuals reporting clinically meaningful symptoms of anxiety was consistently greater than the proportion reporting clinically meaningful symptoms of depression. At any point in time, individuals in each cohort with elevated symptoms of anxiety exhibited lower performance with respect to processing speed, verbal learning, and working memory, even after we accounted for potential confounders. These longitudinal findings are consistent with our prior cross-sectional findings in these same cohorts at their enrollment visit[4] and are consistent with other cross-sectional studies that found anxiety to be associated with lower performance on the SDMT in persons with MS.[2,3]

Within-persons, however, the development of elevated symptoms of anxiety over time was not associated with declines in cognitive performance over time for any of the domains of ability evaluated. By contrast, the development of elevated symptoms of depression within-persons was associated with declines in processing speed for all cohorts studied, as has been consistently demonstrated in populations with major
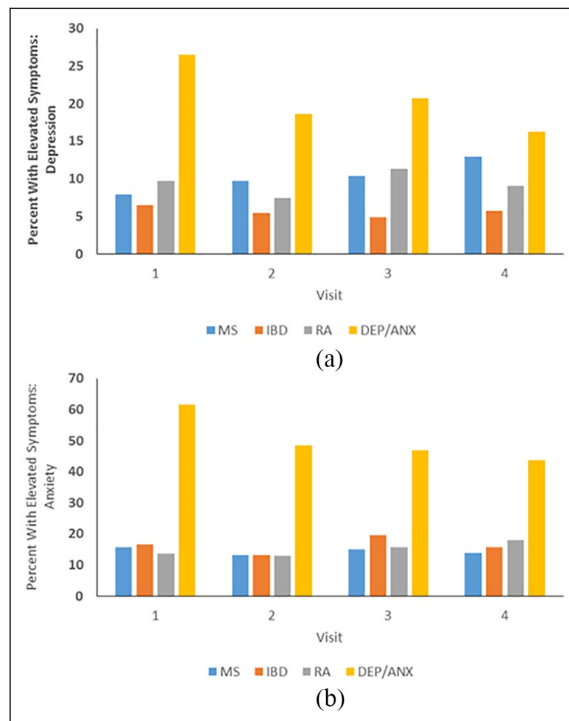
Figure 1. Percentage of participants in each cohort with elevated symptoms of (a) depression and (b) anxiety.
MS: multiple sclerosis; IBD: inflammatory bowel disease; RA: rheumatoid arthritis; DEP/ANX: depressed/anxious.
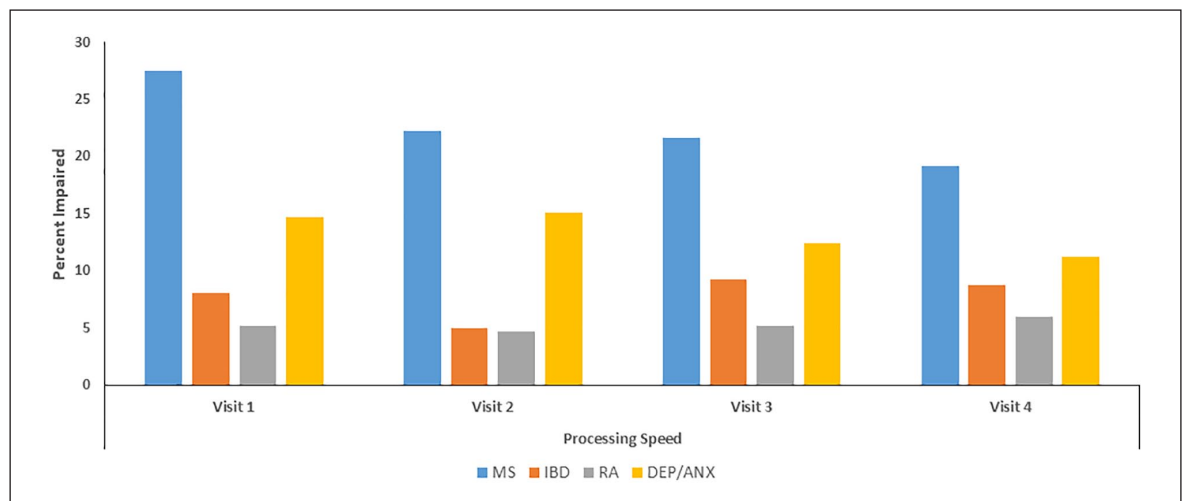
Figure 2. Percentage of participants in each cohort with impaired performance on the symbol digit modalities test at each visit.
MS: multiple sclerosis; IBD: inflammatory bowel disease; RA: rheumatoid arthritis; DEP/ANX: depressed/anxious.

Table 2. Between-individual and within-individual effects of anxiety and depression on cognitive function.[a]

Cognitive domain/test	Cohort	Depression		Anxiety	
		Between-effect (95% CI)	Within-effect (95% CI)	Between-effect (95% CI)	Within-effect (95% CI)
Processing speed (SDMT)[b]	All	−0.25 (−0.51, 0.015)	**−0.12 (−0.21, −0.021)**	**−0.43 (−0.65, −0.21)**	0.0186 (−0.05, 0.087)
	MS, IBD, and DEP/ANX			−0.34 (−0.58, −0.11)	
	RA			**−1.07 (−1.58, −0.55)**	
Verbal learning (CVLT-II)	All	−0.19 (−0.55, 0.16)	0.011 (−0.14, 0.16)	**−0.31 (−0.59, −0.036)**	−0.072 (−0.20, 0.055)
Delayed recall memory (CVLT-II)		−0.10 (−0.43, 0.22)	−0.015 (−0.13, 0.11)	−0.15 (−0.39, 0.092)	−0.0016 (−0.12, 0.086)
Working memory (LNS)[c]		0.14 (−0.10, 0.37)	−0.052 (−0.14, 0.036)	−0.17 (−0.35, −0.0015)	−0.010 (−0.084, 0.063)

MS: multiple sclerosis; IBD: inflammatory bowel disease; RA: rheumatoid arthritis; DEP/ANX: depressed or anxious cohort without MS, IBD, or RA; SDMT: symbol digit modalities test; CVLT: California verbal learning test; LNS: letter number sequencing test.
Boldface indicates statistical significance after application of Benjamini–Hochberg correction.
[a]Adjusted for disease cohort, smoking, body mass index, diabetes, hypertension, and hyperlipidemia.
[b]Interaction between cohort and effect of anxiety where RA differed from other cohorts as shown on next two lines.
[c]LNS models further adjusted for sex and education.

depression.[17] Relatively few longitudinal studies have explicitly examined the relationship between changes in the symptoms of depression or anxiety and subsequent changes in cognition in MS. One retrospective study of 69 persons with MS found that changes in depressive symptoms measured by the Beck Depression Inventory Fast Screen from baseline to follow-up ⩾18 months later were not associated with changes in processing speed, verbal memory, visuospatial memory, verbal fluency, or executive function.[28] This contrasts with our findings and may reflect their smaller sample size, limited change in cognitive performance over the study period, or the use of a different measure of depression symptoms. Anxiety symptoms were not assessed. A study of 38 persons with MS and no major depression disorder (MDD) reported that depressed mood, state anxiety, and negative affect at baseline were associated with worse cognitive performance 1 year later, particularly verbal episodic memory.[29] Notably this association occurred without any between-person (cross-sectional) effect of depression, similar to our findings of a within-person but no between-person effect for depression.

Studies regarding the association between depression, anxiety, and cognition have been even more limited in RA and IBD. In a systematic review of cognition in RA, 14 studies were cross-sectional, while one study assessed test–retest reliability over a 24-hour period;[30] no longitudinal studies were identified. Notably, participants with RA performed worse than healthy controls or as compared to age-related normative values with respect to concentration, judgment, memory, verbal function, and visuospatial function. While no consistent associations with depression or anxiety were identified, the studies reviewed were heterogeneous. In IBD, a few cross-sectional studies have reported mixed findings. One study of 61 persons with Crohn's disease and subjective cognitive complaints or screening test scores suggestive of cognitive decline reported that depressive symptoms were not associated with global cognitive function.[31] Another study suggested elevated symptoms of depression may account for differences in crystallized intelligence between persons with IBD and healthy controls, but this effect was eliminated when differing levels of education between groups was considered.[32]

We observed differences in the association between anxiety and cognition across IMID, with stronger between-person effects occurring in the RA cohort than in the MS, IBD, and DEP/ANX cohorts. The reasons for these differences are uncertain but may reflect inherent differences in the various underlying pathogenic mechanisms leading to cognitive impairment

across IMID disease groups and differences in susceptibility to the impacts of anxiety and depression on cognitive abilities across diseases. A study of 7977 children and adolescents found that greater genetic risk for RA was associated with lower performance intelligence quotient (IQ) and verbal IQ, whereas no such associations were found between polygenic risk scores for MS or IBD and IQ.[33] Notably, this study failed to find associations between polygenic risk scores for RA, MS, or IBD and depression or anxiety at age 18 years. Differences such as this require replication and further evaluation as to their mechanisms. Structural and functional changes in the brain that may underlie cognitive changes in IMID that are not considered primary CNS disorders are also worthy of exploration.

The magnitude of the within-person effects of depression on cognitive tests observed was modest and did not meet the proposed threshold of being clinically meaningful for the SDMT. This may reflect the modest number of participants whose status changed between the presence or absence of clinically meaningful symptoms of depression over time. The 3-year study interval also meant that changes in cognition over time were small, and we may not have used the tests most sensitive to effects of depression. However, it is also important to consider that cognitive deficits associated with depression may not fully remit even when their depressive symptoms fall below clinically significant levels. For example, in the general population, persons with MDD who meet the criteria for remission still have lower performance with respect to processing speed, attention, and memory than healthy controls,[34] and deficits in executive function also persist.[35]

Strengths of this study include the longitudinal design and inclusion of comparison cohorts, namely, IBD, RA, and DEP/ANX, for our MS cohort. Loss to follow-up was small given the 3-year duration, but we preferentially lost participants with elevated depression and anxiety symptoms and worse cognition, potentially reducing the sensitivity of our analysis. Although we could not examine all potentially relevant cognitive domains, we examined those most commonly affected in MS and in persons with depression or anxiety. We used single cognitive tests to assess complex cognitive constructs such as processing speed, rather than multiple tests. Repeated administration of cognitive tests may induce practice effects, but we used alternate test forms when available, and tests were completed 1 year apart. Although formal diagnoses of psychiatric disorders were assessed at enrollment, these were not reassessed at follow-up to limit participant burden. Nonetheless, we used a measure of depression and anxiety symptoms that have been validated for use in all cohorts studied. Also, we previously showed that elevated symptoms of depression were more strongly associated with cognitive performance than a formal diagnosis of major depression.[4]

People with MS have slowed information processing speed as compared to people with other IMID such as IBD and RA and compared to persons with DEP/ANX without MS or other IMID. However, across persons in all cohorts, elevated anxiety symptoms adversely affected information processing. Similarly, within individuals with MS, IBD, RA, or a history of DEP/ANX but no IMID, elevated depression symptoms over time were associated with declines in information processing speed. Our findings have implications for clinicians given that symptoms of anxiety and depression are common in persons with MS and other IMID, but remain underdiagnosed and undertreated.[36] The adverse effects of symptoms of anxiety and depression on outcomes such as quality of life point to the need for routine assessment and management of these symptoms. However, our findings also point to the need for clinical trials to determine whether effective management of anxiety and depression symptoms leads to improvement in cognitive performance and to determine whether the association between these symptoms and cognition is causal.

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Supplemental Material

Supplemental material for this article is available online.

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