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Handedness and Cognition in Multiple Sclerosis: Potential Indications for Hemispheric Vulnerability

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Abstract

Background: Multiple sclerosis (MS) affects over 2.5 million individuals worldwide, yet much of the disease course is unknown. Hemispheric vulnerability in MS may elucidate part of this process but has not yet been studied. The current study assessed neuropsychological functioning as it relates to hemispheric vulnerability in MS.
Methods: Verbal IQ, as measured by verbal comprehension index (VCI), nonverbal IQ, as measured by perceptual reasoning index (PRI) and memory acquisition were compared in right-handed (dextral) and non-right-handed (non-dextral) persons with MS (PwMS).
Results: Linear mixed-effects modeling indicated a significant main effect of handedness, $F(1, 195.35) = 3.95$, $p = .048$, for a composite measure of VCI, PRI, and memory acquisition, with better performance for dextral PwMS. In examining differences for specific neuropsychological measures, the largest effect size between dextral and non-dextral participants was seen in PRI ($d = 0.643$), $F(1,341) = 12.163$, $p = .001$. No significant interaction effect between handedness and IQ was found, $F(3, 525.60) = 0.75$, $p = .523$.
Conclusions: Dextral PwMS perform better than non-dextral PwMS when assessing neuropsychological performance for memory and IQ combined. Results are suggestive of increased vulnerability in the left brain to the pathological process of MS.

Keywords: Multiple Sclerosis; Lateralization; Language & Language Disorders; Intelligence; Assessment; Epilepsy

Introduction

Multiple sclerosis (MS) is a demyelinating disease known to affect physical, emotional, and cognitive functioning (Gold, Schulz, Mönch, Schulz, & Heesen, 2003). The pathological features of MS are consistent with an autoimmune mechanism; however, MS has a predominantly unknown etiology (Gardener, Munger, Chitnis, Spiegelman, & Ascherio, 2009) and is considered neurodegenerative in nature (Farrell, Motl, Learmonth, & Pilutti, 2021). Neurodegeneration can progress asymmetrically, with examples such as unilateral optic nerve inflammation and left-brain gray matter loss (Farrell et al., 2021; Körner et al., 2011; Lubben, Ensink, Coetzee, & Labrie, 2021). Current clinical phenotypes of MS are as follows: 1. Relapse remitting MS (RRMS), the most common MS phenotype, is characterized by relapses, or periods of exacerbations, followed by remitting periods without symptoms (Thompson et al., 2000). Dissemination in space, gadolinium-enhancing lesions, and non-enhancing T2 lesions is present (Vollmer, Nair, Williams, & Alvarez, 2021). 2. Secondary progressive MS typically follows the initial RRMS course with a progression of worsened neurological functioning and an accumulation of disability over time

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(Thompson et al., 2000). 3. Primary progressive MS is characterized by worsening neurological functioning from the onset, without periods of relapses or remission (Montalban et al., 2009). MS is the most common cause of neurological disability among young adults worldwide, with cognitive concerns predominating as a disabling symptom (Chaves et al., 2019).

Although cognitive dysfunction affects~45%–60% of persons with MS (PwMS) (Rao et al., 1991) and is one of the earliest symptoms of disease (Schulz, Kopp, Kunkel, & Faiss, 2006), the etiology of cognitive dysfunction in PwMS is debated (Guimarães & Sá, 2012). There are high levels of variability in cognition across PwMS (Benedict, Amato, DeLuca, & Geurts, 2020) likely due in-part to MS-lesions presenting in both the brain and/or spinal cord (Minagar & Alexander, 2003). Indeed, cognitive dysfunction can appear in domains of processing speed, attention, memory, executive functioning, and visuospatial abilities (Amato et al., 2019). A better understanding of cognitive risk factors for PwMS is imperative, as cognitive dysfunction can negatively affect activities of daily living such as participation in daily life and social activities (Fenu et al., 2018) and may also impede adherence to treatments and one's ability to benefit from rehabilitative strategies (Amato et al., 2019; Goretti et al., 2009).

Patterns of cognition suggestive of lateralized hemispheric vulnerability could elucidate the pathological process of MS, as this pattern has been observed in other neurological populations such as epilepsy (Blackburn et al., 2007) and stroke (Schouten, Schiemanck, Brand, & Post, 2009). Indeed, studies utilizing imaging techniques in PwMS suggest brain asymmetry with an increased vulnerability to the pathological process in the dominant hemisphere (Filippi, Martino, Mammi, Campi, & Comi, 1995; Savio et al., 2015). This is further evidenced by a typically asymmetric lesion distribution, asymmetric gray matter loss in left brain regions, and unilateral inflammation of the optic nerve (Lubben et al., 2021). Although there are some inconsistencies surrounding hemispheric asymmetry in MS, inconclusive results may stem from changes in disease progression over time; characteristic lesions in MS typically have a mildly asymmetric distribution early in disease, but are eventually found bilaterally (Filippi et al., 2019). The utilization of cognitive patterns that are suggestive of hemispheric vulnerability has been utilized to understand disease in other neurological populations; for example, more nonverbal memory deficits have been observed in right-sided epilepsy as compared with left-sided epilepsy (e.g., Abrahams, Pickering, Polkey, & Morris, 1997), and poor verbal recall and recognition have been observed in patients with left hemispheric stroke as compared with right hemispheric stroke (Schouten et al., 2009). Given the evidence for asymmetric vulnerability in MS, as well as the utility of cognitive patterns pointing to hemispheric vulnerability in diseases such as epilepsy and stroke, it is proposed that elucidating patterns of cognition in PwMS could be a useful tool in understanding patterns of disease pathology in MS.

Handedness is one factor that may help elucidate hemispheric vulnerability in PwMS. Hand preference has been directly associated with interhemispheric lesion distribution (Filippi et al., 1995) in PwMS such that those who are more right-handed (RH) have a relatively larger right-sided lesion volume (supported by a positive Spearman correlation), as compared with PwMS who are relatively more left-handed (LH) and thus have a comparatively greater left-sided lesion volume. Furthermore, a 62% increased risk of MS has been found among women who are naturally LH, as compared with those who are naturally RH (Gardener et al., 2009). Left handedness has also been associated with other poor health outcomes such as, low birth weight (Heikkilä et al., 2018), Crohn's disease, asthma, attention deficit hyperactivity disorder, allergies, migraine, and myasthenia gravis (Bryden, McManus, & Bulman-Fleming, 1994). In terms of cognition, varying handedness profiles have been associated with different neuropsychological outcomes on measures such as the California Verbal Learning Test-2nd edition (CVLT-II), where inconsistent (i.e., lack of hand preference) RH individuals recalled and recognized more words and showed better source recognition, than consistent RH individuals (Chu, Abeare, & Bondy, 2012). In terms of intelligence quotient (IQ), left versus right mesial temporal lobe epilepsy has been associated with relative deficits in verbal versus nonverbal intelligence, respectively (Kim, Yi, Son, & Kim, 2003). Conversely, the relationship between handedness and IQ has not yet been examined in PwMS. Thus, we utilized the current study to address this gap in the literature by examining a potential relationship between handedness and IQ among PwMS.

Studies suggest that a more vulnerable left hemisphere exists among people with epilepsy (Dean, Solomon, Harden, Papakostas, & Labar, 1997; Gatzonis et al., 2002; Paolozzi, 1969), particularly in non-dextral persons (Holmes, Dodrill, Kutsy, Ojemann, & Miller, 2001), and that persistent, early, left-sided seizure damage can result in functional reorganization toward the right hemisphere (Giza, Prins, Hovda, Herschman, & Feldman, 2002), particularly during infancy (Taylor, 1969). Functional reorganization leading to subsequent overcrowding of the right hemisphere may result in a naturally RH person becoming LH (Satz, 1972; Satz, Strauss, Hunter, & Wada, 1994). This phenomenon labeled, "pathological left-handedness," more frequently coincides with right-sided language dominance (Knecht et al., 2000; Loring et al., 1990; Rasmussen & Milner, 1977; Vargha-Khadem, O'Gorman, & Watters, 1985) as well. However, the recovery of endangered functions may result in faulty connections (Giza et al., 2002); in pediatric populations, left-sided damage may not only shift handedness, but may also lead to a shift in functional abilities toward the right hemisphere, inhibiting some right-sided cognitive functioning, such as nonverbal abilities (Lansdell, 1969), to spare language. The resulting cognitive pattern has shown that "pathological" left handers have a split between verbal and nonverbal skills, in favor of verbal skills (Lansdell, 1969).

Better localization of MS pathology and its course could then enable improved and targeted treatment interventions. Developing a better understanding of MS and improving treatment interventions is of particular importance given that PwMS typically report worse quality of life than the general population (Amtmann, Bamer, Kim, Chung, & Salem, 2018; Pittock et al., 2004). This lower quality of life may be in part due to difficulty adapting to the range of physical, cognitive, and emotional symptoms that present with MS (Gold et al., 2003).

Given previous studies on handedness and cognition in PwMS (i.e., the CVLT-II; Chu et al., 2012) and in epilepsy (i.e., IQ; Kim et al., 2003), and the fact that a potential relationship between IQ and handedness has not yet been explored in PwMS, this study aimed to explore a potential relationship between handedness and cognition (i.e., IQ and memory), among a sample of adult PwMS. The primary aim was to assess whether a cognitive pattern in favor of verbal skills over nonverbal skills across domains of IQ and memory would emerge, which could represent pathological left-handedness and increased left-sided brain vulnerability in PwMS. We expected to observe comparatively increased vulnerability to the left-hemisphere in PwMS, as has been observed across neurological populations such as, epilepsy, stroke (Blackburn et al., 2007; Schouten et al., 2009), Alzheimer's disease, and Huntington's disease, (Janke et al., 2001; Lambrecq et al., 2013; Thompson et al., 2001, 2003). A more vulnerable left hemisphere has been suggested in MS as well (Lubben et al., 2021; Preziosa et al., 2017; Prinster et al., 2006) and we suspect that this potential left-sided vulnerability to MS disease pathology would result in a cognitive pattern in favor of verbal skills over nonverbal skills.

Methods

The current retrospective study used data from an archival neuropsychological database of physician-confirmed PwMS (McDonald et al., 2001). All participants consented (with an IRB-approved consent form) to participate in the research and data included in this study were collected from February 2001 to December 2018. The study was approved by the institutional review board at the Albert Einstein College of Medicine (Bronx, New York).

Participants

Because ~85% of PwMS are diagnosed with RRMS (Nicholas, Electricwala, Lee, & Johnson, 2019), this study aimed to evaluate patterns of handedness specifically in this selection of PwMS. Therefore, eligibility criteria included having a diagnosis of clinically definite RRMS, being age 18 years or older, and being fluent in English, to mitigate language confounds on neuropsychological testing. Participants were excluded if they were on a high-dose corticosteroid or experiencing a clinical exacerbation at the time of the interview.

Procedures

The neuropsychological evaluation was performed at an MS center outside of a large-metropolitan area. Patients completed a clinical interview, battery of neuropsychological tests, and self-report measures. The neuropsychological measures were administered using standard administration protocols.

Measures

Demographics. Age, sex/gender, education, and race/ethnicity were recorded via self-report. For race/ethnicity, participants were asked to select from the following three options: White, Black, and Hispanic/Latinx/other. The Black and Hispanic/Latinx/Other groups were combined to form two race/ethnicity groups: White and non-White. The number of years carrying an MS diagnosis was obtained from each patient's medical record.

Handedness. Self-report was utilized to assess handedness. Participants were asked, "are you right- or left-handed?" during the clinical interview portion of their neuropsychological evaluation. Given that human handedness was originally theorized to be influenced by an inherited factor, in which a shift toward the right was described as "dextral" and some genetic factor pushes the distribution of chance for handedness into the "dextral" direction (Annett, 1994), those who were RH were categorized as "dextral," whereas all other handedness patterns (i.e., mixed or left-handedness) were coded as "non-dextral."

Cognition. **Wechsler Intelligence Scales**. Given the longevity of the archival database used in this study, several versions of Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Abbreviated Scale of Intelligence (WASI) were used for this sample to assess IQ, including the WAIS-r, the WAIS-III and the WAIS-IV, the WASI, and the WASI-II. All WAIS measures examine IQ both at the composite and subscale level; they are reliable and valid (Wechsler, 1981; Narrett, 1984; Snowden, 2004; Wechsler, 2008; Silva, 2008; Wechsler, 2011; McCrimmon & Smith, 2013), pencil-and-paper measures, comprised of visual and auditory stimuli assessing domains of verbal abilities, perceptual reasoning, working memory, and processing speed functioning.

A strong correlation exists across several subtests of the WAIS throughout its different iterations. Specifically, the verbal IQ (VIQ) subtest of the WAIS-III and Verbal Comprehension Index (VCI) subtest of the WAIS-IV have a correlation of 0.89 (Coalson, Raiford, Saklofske, & Weiss, 2010) and the performance IQ (PIQ) subtest of the WAIS-III and Perceptual Reasoning Index (PRI) subtest of the WAIS-IV have a correlation of 0.83 (Coalson et al., 2010). This study performed additional analyses by evaluating standard scores of composite variables across versions to ensure that the composites could be combined into one verbal intelligence composite (VIQ and VCI) and one visual intelligence composite (PIQ and PRI) for the purposes of data analysis. Preliminary analyses confirmed that the VIQ ($M = 104.32$, $SD = 15.34$) and VCI ($M = 137$, $SD = 16.07$) were comparable between measures $t(25.6) = -0.840$, $p = .409$. Similarly, PIQ ($M = 96.14$, $SD = 11.98$) and PRI ($M = 95.56$, $SD = 15.58$) measures were comparable with no significant difference between the measures $t(26) = 0.576$, $p = .570$. Therefore, the final composites for verbal and visual intelligence were combined and renamed VCI and PRI, respectively.

California Verbal Learning Test. The CVLT-II provides a measure of verbal memory. Participants are read 16 words aloud and are asked to recall as many as possible over several learning trials, a short-delay, and a long-delay recall (Delis et al., 2000). The CVLT-II is a reliable and valid measure that has been utilized extensively in the MS population (Benedict, 2006). It has been specifically chosen by an expert panel on MS for its validity in evaluating verbal memory deficits in the MS population (Benedict et al., 2002) and has thus been included in several cognitive screeners for MS such as, the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) (Benedict et al., 2006). Only the learning trials of the CVLT-II have been incorporated into cognitive screeners for MS such as, the Brief International Cognitive Assessment for MS (BICAMS) (Benedict et al., 2012), as PwMS typically have more dysfunction in memory acquisition rather than memory storage (Rao et al., 1993; Sandry, Zuppichini, Rothberg, Valdespino-Hayden, & DeLuca, 2019) and the literature supports that delayed memory either improves, or is equal to, that of healthy controls after PwMS are provided with multiple opportunities to learn new information (e.g., Burns, Davidson, Zaslofsky, Parker, & Maki, 2017; Deluca, Barbieri-berger, & Johnson, 1994). Thus, this study also exclusively analyzed the learning trials of the CVLT-II.

Brief Visuospatial Memory Test. The Brief Visuospatial Memory Test-revised (BVMT-r) is a measure of nonverbal memory. Participants are presented with a page of six figures and are asked to study the page for 10 s, noting the details of each shape and its location on the page. The participants are then asked to reproduce as many figures as possible from memory over three learning trials and after a delay (Benedict et al., 1996). The BVMT-r has good reliability and validity (Benedict et al., 1996). This test was specifically chosen as a measure of nonverbal memory given its validity in the MS population (Benedict et al., 2012; Gromisch, Portnoy, & Foley, 2018) and its utility in several MS-cognitive screeners such as, the BICAMS (Benedict et al., 2012; Langdon et al., 2012) and the MACFIMS (Benedict et al., 2006).

Disability. The Incapacity Status Scale (ISS) is a 16-item questionnaire, each rated on a 0–4 scale ranging from 0, or no incapacity, 1, performance is impaired but accomplished without aid, 2, mechanical aids are required, 3, human assistance is required, and 4, when performance is lost. Items are summed for a total score ranging from 0 to 64 (higher scores indicate greater disability). Questions assess disability across multiple domains including stair climbing, ambulation, toilet/chair/bed transfer, bowel function, bladder function, bathing, dressing, grooming, feeding, vision, speech and hearing, medical problems, mood and thought disturbances, mentation, fatigability, and sexual function (Kurtzke, 1984). The ISS is highly correlated ($r = 0.86$) (Izquierdo et al., 1991) with the expanded disability status scale, which is primarily used to quantify MS-related disability at the clinical level (Provinciali et al., 1999; Slater et al., 1984).

Data analysis plan

Statistical analyses were conducted using IBM SPSS Statistics v.25. Descriptive statistics were run to characterize the sample with *t* tests used to assess differences for dichotomized variables. Participants ($N = 429$) were those that remained from the original sample ($N = 584$) after listwise deletion for missing data. Descriptive statistics were run to assess missing data after pairwise deletion for each neuropsychological outcome. Pearson and Spearmen bivariate correlations were conducted to assess relationships between neuropsychological test variables.

Table 1. Descriptive statistics: participant demographics

	Total ($N = 429$)		Dextral ($n = 390$)		Non-Dextral ($n = 39$)		
Demographic variable	*n*	%	*n*	%	*n*	%	*p* value
Sex/Gender							.682
Female	325	75.8%	297	76.2%	28	71.8%	
Male	104	24.2%	93	23.8%	11	28.2%	
Race/ethnicity							.267
White	407	68.4%	277	71.0%	32	82.1%	
Non-White	91	15.3%	70	17.9%	4	10.3%	
Education Years							.191
≥ 12 yrs	308	71.8%	284	72.8	24	61.5	
< 12 yrs	121	28.2%	106	27.2	15	38.5	
	M, Mdn	*SD, [IQR]*	*M, Mdn*	*SD, [IQR]*	*M, Mdn*	*SD, [IQR]*	*p* value
Age (years)	46.8	11.2	47.0	11.3	45.9	10.9	.573
Disease Duration from MS length Dx (years)	8	[3,20]	8	[1,15]	7	[1,15]	.641
ISS	11.2	6.4	11.3	6.3	12.1	6.7	.520

Note: FSIQ = full scale intelligence quotient; Length Dx = duration of MS diagnosis; ISS = incapacity status scale total score. Non-White participants were ones who reported their race/ethnicity as Black or Hispanic/Latinx/Other.

Data analyses of handedness in relation to neuropsychological domains were performed using linear mixed-effects modeling (LMM) given that the neuropsychological data (repeated measurements) were correlated within an individual. Multiple LMM's were utilized to examine differences in dextral and non-dextral individuals across the following neuropsychological domains: (1) intelligence (IQ): VCI (verbal) and PRI (nonverbal); and (2) memory acquisition: CVLT-II total learning (verbal) and BVMT-r total learning (nonverbal). The predictor variable, "Handedness," had two levels: dextral PwMS and non-dextral PwMS. The outcome variable, labeled "Neuropsychological Test," was comprised of the VCI, PRI, CVLT-II total learning, and BVMT-r total learning scores. Analyses were adjusted for demographic variables including age, sex/gender, education, ethnicity, MS-related disability (via the ISS), and years carrying an MS diagnosis; standardized scores were not readjusted for age or sex/gender when applicable (i.e., when scores were already adjusted for age or sex/gender).

As mentioned, multiple LMM's were utilized: Model 1 (the null model) included the random intercept of participant without any fixed effects. Model 2 added the Neuropsychological Test variable, Model 3 added Handedness as a fixed factor, and Model 4 added the interaction term of Handedness × Neuropsychological Test. Finally, Model 5 examined the interaction of Handedness × Neuropsychological Test after adjustment for the demographic variables listed earlier.

Results

Participants were predominantly middle-aged, White women, of average intelligence, the majority of whom had at least a high school education (see Table 1). Of the total sample ($N = 429$), 90.9% ($n = 390$) were dextral. Dextral and non-dextral participants did not differ on demographic variables (see Table 1). Table 2 displays descriptive statistics of the demographically adjusted T-scores for the neuropsychological variables. Higher verbal intelligence for the total sample was associated with higher verbal, nonverbal learning, verbal learning, and perceptual reasoning abilities (see Table 3). This pattern was also seen for dextral participants. Conversely, for non-dextral participants, higher verbal intelligence was associated with higher perceptual reasoning abilities. Neither verbal intelligence nor perceptual reasoning abilities were associated with memory abilities.

See Table 4 for results of the LMMs to examine differences in dextral and non-dextral individuals across neuropsychological domains. In Model 1 (the null model), participant accounted for a significant portion of the variance in the outcome variable, Neuropsychological Test (intraclass correlation coefficient = 0.45, $p < .001$). In Model 2, Neuropsychological Test was added as a fixed effect, which did not significantly improve the model fit, $F(3, 1040.61) = 0.07$, $p = .974$, from Model 1 to Model 2 (Δ-2LL = 0.22, $\Delta df = 3$, $p = .97$). The model fit (Δ-2LL = 35.72, $\Delta df = 1$, $p < .001$) was improved in Model 3, after handedness was added as a fixed factor; a significant, main effect of handedness, $F(1, 431.17) = 8.06$, $p = .005$, resulted. Model 4 added the interaction term of Handedness × Neuropsychological Test, which did not significantly improve the model fit (Δ-2LL = 3.19, $\Delta df = 3$, $p = .36$), and the interaction term was not significant $F(3, 1026.73) = 1.07$, $p = .363$. Finally, Model 5, which examined the interaction of Handedness × Neuropsychological Test after adjustment for demographic variables, showed improved fit (Δ-2LL = 1804.03, $\Delta df = 1$, $p < .001$).

Table 2. Descriptive statistics: neuropsychological tests

	Total ($N = 429$)		Dextral ($n = 390$)		Non-dextral ($n = 39$)		
Neuropsychological variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*p-value*
FSIQ	98.36	15.04	97.89	14.51	100.53	16.70	.323
VCI	99.27	15.15	99.55	15.35	96.80	13.25	.055
PRI	95.86	14.41	96.57	14.13	89.03	15.63	<.001
CVLT-II Learning	45.44	12.54	45.94	12.44	41.66	12.12	<.001
BVMT-r Learning	51.91	13.08	52.17	13.00	49.56	13.43	.026

Note: VCI = verbal composite index; PRI = perceptual reasoning index; CVLT-II = California Verbal Learning Test-2nd edition, Learning Score; BVMT-r = brief visual memory test, revised, learning score. Scores are demographically adjusted T scores.

Table 3. Bivariate relationships: total, dextral, and non-dextral samples

	1	2	3	4
Total sample				
1. VCI	—	—	—	—
2. PRI	0.58***	—	—	—
3. CVLT-II	0.38***	.54[1]***	—	—
4. BVMT-r	.31[1]***	.29[1]***	0.19***	—
Dextral sample				
1. VCI	—	—	—	—
2. PRI	.53[1]***	—	—	—
3. CVLT-II	0.37***	.37[1]***	—	—
4. BVMT-r	.18[1]***	.28[1]***	0.17***	—
Non-dextral sample				
1. VCI	—	—	—	—
2. PRI	.66[1]***	—	—	—
3. CVLT-II	0.46 (0.009)	.12[1] (0.525)	—	—
4. BVMT-r	.18[1] (0.359)	.37[1] (0.046)	0.28 (0.095)	—

Note: [1]Spearman's rho values; all other values are Pearson *r*; *p* values are listed in parenthesis; VCI = verbal composite index; PRI = perceptual reasoning index; CVLT-II = California Verbal Learning Test-2nd edition Learning Score; BVMT-r = brief visual memory test, revised, learning score; *** $p < .001$.

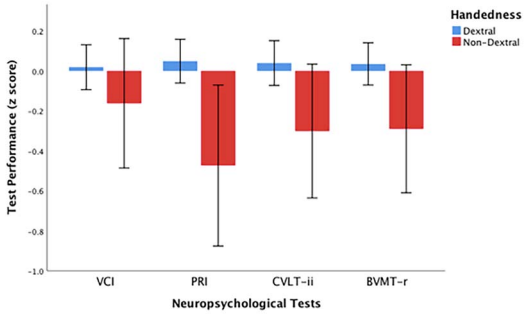
Table 4. LMEM models: verbal and nonverbal outcome measures with handedness

	Model 1				Model 2				Model 3				Model 4				Model 5			
	B	*SE B*	*t*	*p*	*B*	*SE B*	*t*	*p*	*B*	*SE B*	*t*	*p*	*B*	*SE B*	*t*	*p*	*B*	*SE B*	*t*	*p*
Intercept	0.00	0.04	−0.10	.919	0.00	0.05	−0.06	.954	−0.36	0.13	−2.59	.010	−0.36	0.17	−2.19	.029	−0.38	0.25	−1.50	.133
VCI					−0.01	0.06	−0.24	.811	−0.14	0.06	−0.25	.797	0.18	0.19	0.95	.343	0.17	0.29	0.59	.559
PRI					−0.00	0.06	−0.10	.921	−0.01	0.06	−0.13	.893	−0.13	0.19	−0.70	.483	−0.15	0.29	−0.53	.596
CVLT-II					0.01	0.06	0.24	.813	0.01	0.06	0.22	.824	0.06	0.18	0.33	.742	0.22	0.28	0.79	.432
BVMT-r					0[a]	0	—	—	0[a]	0	—	—	0[a]	0	—	—	0[a]	0	—	—
							F	*p*			*F*	*p*			*F*	*p*			*F*	*p*
Test							0.07	.974			0.08	.972			0.68	.563			0.72	.542
Handedness											8.06	.005			8.02	.005			3.95	.048
Interaction															1.07	.363			0.75	.523
-2LL[b]	3726.71				3726.49				3690.77				3687.58				1883.55			
Estimated Parameters	3				6				7				10				10			

Note: Model 1 ($N = 1{,}417$) is the null model; Model 2 ($N = 1{,}417$) is an unadjusted model with the addition of the Neuropsychological Test variable; Model 3 ($N = 1{,}406$) is an unadjusted model with the addition of the handedness variable; Model 4 ($N = 1{,}406$) is an unadjusted model with the addition of the Handedness × Neuropsychological Test interaction; Model 5 ($N = 718$) is a demographically adjusted model with the Handedness × Neuropsychological Test interaction; VCI = verbal composite index; PRI = perceptual reasoning index; CVLT-II = California Verbal Learning Test, −2nd edition, learning score; BVMT-r = brief visual memory test, revised, learning score; z-scores are reported.

[a]This parameter is set to 0 because it is redundant. [b]-2 log-likelihood is a measure of how well the model fits the data (a better fit is indicated by smaller numbers).

Although the interaction term in Model 5 was not significant, $F(3, 525.60) = 0.75$, $p = .523$, a main effect of handedness remained, $F(1, 195.35) = 3.95$, $p = .048$, such that dextral (D) participants outperformed non-dextral (ND) participants on measures of VIQ ($M_D = 0.006$, $SD_D = 0.055$; $M_{ND} = -0.186$, $SD_{ND} = 0.174$), verbal memory acquisition ($M_D = 0.047$,



Note. Error bars represent 95% CI. VCI = Verbal Composite Index; PRI = Perceptual Reasoning Index; CVLT-II = California Verbal Learning Test-2nd edition, Learning Score; BVMT-r = Brief Visual Memory Test, revised, Learning Score.

Fig. 1. Bar graph representing neuropsychological test performance by handedness. *Note.* Error bars represent 95% CI. VCI = verbal composite index; PRI = perceptual reasoning index; CVLT-II = California Verbal Learning Test-2nd edition, Learning Score; BVMT-r = brief visual memory test, revised, learning score.

$SD_D = 0.055$; $M_{ND} = -0.305$, $SD_{ND} = 0.165$), non-verbal ($M_D = 0.045$, $SD_D = 0.055$; $M_{ND} = -0.497$, $SD_{ND} = 0.174$), and non-verbal memory acquisition ($M_D = 0.040$, $SD_D = 0.053$; $M_{ND} = -0.365$, $SD_{ND} = 0.167$). Figure 1 depicts neuropsychological performance based on handedness.

In a brief follow-up analysis to more closely examine the main effect of handedness on the Neuropsychological Test variable, the largest effect size between dextral and non-dextral participants was seen in the PRI measure ($d = 0.643$), representing a medium-large effect size (see Fig. 1). As previously mentioned, dextral participants performed relatively better than non-dextral participants on the PRI measure of non-verbal. This effect is compared with a small-medium effect size between dextral and non-dextral participants on the VCI measure of VIQ ($d = 0.322$) and on the BVMT-r measure of nonverbal memory (; $d = 0.356$), as well as a small effect size between dextral and non-dextral participants on the CVLT-ii measure of verbal memory (; $d = 0.213$).

Discussion

The current study examined hemispheric vulnerability by looking at patterns of cognition and handedness. Results showed a significant main effect of handedness when verbal and non-verbal and memory acquisition measures were combined, with better performance for dextral participants overall compared with non-dextral participants. However, there was no significant interaction between handedness and the Neuropsychological Test variable. Although there was no statistically significant relationship between handedness and each component of the IQ measure, a medium-large effect size was found for the relationship of handedness and PRI: non-dextral PwMS performed relatively worse on non-verbal measures, as compared with VIQ measures, and this was the largest effect size with regard to the relationship of handedness and the IQ measures. The relationship between handedness and PRI warrants further exploration in future research particularly given that to date, there have not been any studies evaluating IQ as it relates to handedness in PwMS.

The medium-large effect with regard to handedness and non-verbal seen in this study (with non-dextral PwMS performing worse than dextral PwMS on measures of nonverbal functioning), indicating a relative preservation of verbal skills, is similar to results in non-dextral epilepsy populations (Holmes et al., 2001). It is therefore possible that pathological left handedness/crowding, and an increased vulnerability to the left hemisphere in PwMS, could exist. Our speculations are further supported by the following: (1) The current findings are likely novel to the MS brain given that conclusions on handedness and cognition in the general healthy population are mixed and do not suggest strong evidence of an effect of handedness on IQ (e.g., Kong et al., 2018; Ntolka & Papadatou-Pastou, 2018; Papadatou-Pastou, 2018). With that said, we acknowledge that there are some studies suggesting significant, though negligible, differences in cognition as it relates to handedness (e.g., Kong et al., 2018; Ntolka & Papadatou-Pastou, 2018; Somers, Shields, Boks, Kahn, & Sommer, 2015). (2) Prior research supports a more vulnerable left hemisphere in MS (Lubben et al., 2021; Prinster et al., 2006) that particularly relates to clinical decline (Preziosa et al., 2017). Once again, there is some inconsistent support for hemispheric asymmetry; however, we speculate this is likely due to the nature of disease progression, as there is an increase in bilateral involvement over time (Filippi et al., 2019). (3) Prior research supports a preferentially vulnerable left hemisphere in other neurodegenerative diseases such as Alzheimer's disease (Janke et al., 2001; Thompson et al., 2001, 2003) and Huntington's disease (Lambrecq et al., 2013). In sum, although neither a more vulnerable left hemisphere nor a shift towards pathological left-handedness can be confirmed without longitudinal imaging

data, we raise the possibility that PwMS have a more vulnerable left hemisphere and that at least a subset of non-dextral PwMS experienced brain reorganization resulting in pathological left-handedness.

A significant interaction between handedness and test was not found, which may be explained in part by the neuropsychological measures used. Although the measures in this study are substantiated in the MS population (Benedict et al., 2012), studies in epilepsy have shown that the CVLT does not lateralize language as well as other verbal learning measures (Loring et al., 2008) and that the BVMT-r has typically been unable to discriminate right- versus left-sided epilepsy (Barr, Morrison, Zaroff, & Devinsky, 2004). Thus, it is possible that these measures were not reliable in lateralizing performance in this study. Furthermore, memory is a complicated construct that is a difficult tool for discriminating lateralized functionality as exemplified by data indicating that novel and familiar words are activated by different brain regions (Johnson, Saykin, Flashman, McALLISTER, & Sparling, 2001). Other evidence indicates that the CVLT-II utilizes both the right hippocampus and right frontal lobe for word learning and retrieval (Johnson et al., 2001), therefore making it a difficult tool to rely on for hemispheric lateralization. Despite limitations in the neuropsychological measures utilized in this study, previous literature on handedness in people without MS does not consistently point to a main effect of handedness (e.g., Sahu et al., 2016; Briggs, Nebes, & Kinsbourne, 1976), thus findings from the current study suggest something novel about the MS brain differentiating it from the brains of people without MS.

Limitations and future directions

A primary limitation of this study is a dearth of neuroimaging, both structural and functional, which would be helpful in corroborating the theories presented here. Procedures such as intracarotid amobarbital (Wada), for example, may be useful in localizing functional brain areas (Rasmussen & Milner, 1977; Spencer, Morrell, & Risinger, 2000) to support findings from this study. Functional imaging studies may also corroborate handedness and its correlation to the dominant hemisphere. In addition, future research would benefit from including a non-MS population as a comparison group. Although it is unlikely that the same pattern would be found in the general healthy population given that the literature on handedness in people without MS does not consistently point to a main effect of handedness (e.g., Sahu et al., 2016; Briggs et al., 1976), this comparison would confirm that the observed pattern is specific to PwMS.

A secondary limitation is that self-report was used to differentiate dextral from non-dextral individuals (Coren, 1993), which does not account for degree of handedness, nor does it account for PwMS who may have had to switch hands due to disease or other factors and therefore may have unique brain compositions. Degree of handedness, for example, has been strongly associated with functional brain specialization (Isaacs, Barr, Nelson, & Devinsky, 2006). Self-report measures also may create errors in accuracy, due to either unconscious misrepresentations of one's history, or perhaps due to patient hesitancy. To compensate for the lack of formal questionnaires, "non-dextral" terminology was utilized to encompass a wider scale of non-RH persons. Future studies may additionally consider including formal handedness measures, such as the Edinburgh Handedness Inventory (Oldfield, 1971), to better categorize and standardize handedness in participants.

A third limitation is the imbalance in sample size. Interpretation of these results is limited by large confidence intervals in the non-dextral population. This is a consequence of having far fewer non-dextral participants than dextral participants in this study sample. Although this sample composition is consistent with the fewer number of non-dextral than dextral individuals in the general MS population (Shirani, Cross, Naismith, & Investigators#, for the M. S. P. A. T. and H. S., 2019), this imbalance continues to be a limiting factor in handedness studies. Therefore, future studies with larger sample sizes of non-dextral participants are recommended (e.g., with targeted recruiting of non-dextral individuals).

Generalizability is a fourth limitation of this study. The sample only included adult patients who were diagnosed with RRMS. This phenotype of MS was chosen because it represents the majority of the MS population; however, it may limit generalizability of the findings to other phenotypes. Similarly, data were collected only in one geographic area with the inclusion of predominantly middle-aged, White women, of average intelligence, the majority of whom had at least a high school education which may limit generalizability to other demographic subgroups. Thus, future studies should consider recruiting a sample with more diverse demographics to increase generalizability.

In addition, there are some limitations regarding the IQ measures used in this study. Firstly, the subtests that comprise the PRI and VCI composite scores were unable to be evaluated individually. Thus, it is unknown whether a particular subtest may be driving the large effect size between dextral and non-dextral groups. Secondly, despite strong correlations between subtests across WAIS versions (as described in the Methods section), using different versions of WAIS within the study sample may have introduced some bias into the results of this study. Future studies would benefit from utilizing the same version of the WAIS throughout all analyses and may consider performing separate analyses on IQ subtests by handedness to see if any main effects emerge. Other aspects of the WAIS, such as a global assessment component that takes memory into consideration, may be considered for future analyses as well.

Other factors that affect cognition are also suggested for future studies. For example, cognition may fluctuate in response to mood, as symptoms of depression and anxiety have been shown to affect cognitive performance across the lifespan (Dotson et al., 2014) as well as in MS specifically (Whitehouse et al., 2019). This is particularly important given that the prevalence rate for major depressive disorder is ∼54% in PwMS and the prevalence rate for clinically significant anxiety is ∼22% in PwMS (Marrie et al., 2015). Furthermore, several mood-stabilizing medications that PwMS may be taking can affect cognition (e.g., Saeedi, Remington, & Christensen, 2006; Wadsworth, Moss, Simpson, & Smith, 2005) and future studies may want to consider adjusting for mood and mood-stabilizing medications.

The current study is substantiated on theories of crowding and pathological left-handedness that are attributed to reorganization during the early stages of life (e.g., Lansdell, 1969; Satz, 1972; Satz et al., 1994). Given that the current sample analyzed adults only, future studies may consider including (or focusing exclusively on) a pediatric MS sample. With that, we speculate that despite the emergence of several neurologic diseases or disorders in adulthood, such as MS, neurological underpinnings of disease may exist during earlier development. Indeed, studies suggest an association between early childhood interventions and reduced probability of MS emergence in adulthood (Black et al., 2021). In addition, certain adult-onset seizure disorders (e.g., idiopathic generalized epilepsy) have genetic correlates (Marini, King, Archer, Newton, & Berkovic, 2003) and in Alzheimer's disease, outcomes have been shown to be affected by early life interventions (Oveisgharan et al., 2020; Calderón-Garcidueñas et al., 2018) as well. Thus, the presence of juvenile correlates is possible and should be explored in additional research. This research on pediatric samples should be done along with continued research on adult samples as brain reorganization has been observed not just in adolescence but even in adult-acquired injuries such as stroke or traumatic brain injury (Hamilton, Chrysikou, & Coslett, 2011; Han, Chapman, & Krawczyk, 2018).

In sum, this study analyzed neuropsychological profiles of dextral and non-dextral PwMS, which could be suggestive of hemispheric vulnerability. The premise of this study consisted of pathological left-handedness and crowding theories that have been substantiated in pediatric epilepsy and in other neurological populations, along with data suggesting worse health outcomes in LH people. Results indicated a significant main effect of handedness when verbal and non-verbal and memory acquisition measures were taken together, with better performance for dextral participants compared with non-dextral participants. The largest effect size was found for PRI such that non-dextral PwMS performed relatively worse on non-verbal measures, as compared with VIQ measures. This relative preservation of VIQ skills is similar to the pattern observed in pathological left handedness profiles of other neurologic populations; this pattern may suggest that PwMS could be susceptible to a more vulnerable left hemisphere, which may in part be explained by pathological left handedness and crowding. Elucidating hemispheric vulnerability in PwMS may help to not only improve understanding of disease, but also to focus research, improve clinical interventions, and generally increase quality of life for PwMS.

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Declaration of Interest

None.

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Conflict of interest

The authors declare that they have no conficts of interest.

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