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Review Article

Association between Non-Right-Handedness and Multiple Sclerosis

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Abstract

Background: Only two studies have examined the relationship between handedness and Multiple Sclerosis (MS).

Objective: To extend previous work examining any relationships between MS and handedness.

Methods: Using an online survey, people with either self-reported Primary Progressive MS (PPMS) or Relapsing Remitting MS (RRMS) (N = 188) were examined. Handedness was categorized three ways using the Edinburgh Handedness Inventory (1971): Writing Hand, Handedness Direction and Handedness Degree.

Results: The interaction between MS Type and Writing Hand was significant such that participants who wrote with their left hand were more likely to be diagnosed with PPMS than participants who wrote with their right hand. The interaction between MS Type and Handedness Direction was significant such that left-handed women were more likely to be diagnosed with PPMS than right-handed women.

Conclusion: The current study suggests that there in fact, may be a relationship between MS and handedness, particularly in women.

Keywords: Multiple Sclerosis; Handedness; Handedness Classification; Primary Progressive Multiple Sclerosis; Relapsing Remitting Multiple Sclerosis; Autoimmune Disease; Hand Preference

Introduction

Only two studies, to our knowledge, have examined the relationship between individual differences in handedness and Multiple Sclerosis (MS). Gardener, et al., examined the association between left-handedness and MS in 121,701 female nurses from the ongoing Nurse's Health Study (NHS) in the United States, with follow-ups from 1976 to 2002 [1]. The nurses were asked to self-report natural hand preference from four choices: right, left, ambidextrous or forced to change. During follow-up, 210 cases of MS were confirmed. A 62% increase in risk of MS was observed among naturally left-handed women compared to naturally right-handed women.

Shirani, Cross and Naismith investigated the relationship between MS and handedness in clinically diagnosed MS patients [2]. Data from the Multiple Sclerosis Partners Advancing Technology Health Solutions network (MS PATHS) (N = 9,618) was examined. Handedness data was available for 8,888 patients, of which 917 (10.3%) were left-handed. Handedness data in the MS PATHS was collected by asking the patients with which hand they wrote [2]. Subjects self-reported either Left-Handed (LH) or Right-Handed (RH) writing hand preference. Overall, Shirani, Cross and Naismith did not observe any evidence to suggest a relationship between individual differences in writing hand and MS.

Gardener, et al., reported that left-handed women may be more likely to develop MS than are right-handed women, while Shirani, Cross and Naismith found no association between MS and individual differences in handedness [1,2]. It is unclear why

these studies differed in their findings; however, one possibility is the difference in definition of handedness. Gardener, et al., used self-reported natural hand preference (right, left, ambidextrous) [1]. Shirani, Cross and Naismith used the participant's self-reported writing hand [2]. In attempts to reconcile the results, we examined handedness-MS relationships using the Edinburgh Handedness Inventory [3]. Handedness literature has indicated that individual differences in hand preference can be categorized directionally (e.g. left vs right) and according to degree (consistent preference for one versus the other hand versus inconsistent hand preference) [4]. In sum, given the differences between the studies, we suggest that it is important to clearly determine handedness measures a priori in order to enable both methodological rigor and replicability.

The current study investigates the relationship between Relapsing Remitting MS (RRMS) and Primary Progressive MS (PPMS) and handedness using writing hand, direction, and degree of hand preference. The aim of the study was to investigate whether there is an association between MS and handedness.

Material and Methods

Participants were required to be 18 years old or older and have self-reported clinically definite MS. As part of a larger study, individuals were recruited online via the internet and social media using sites specifically relevant to the MS community. From October 17, 2019 to August 9, 2021, 269 participants took the survey. Of those participants, only those who i. stated they received a clinical diagnosis of MS from their doctor, listed diagnostic criteria and their MS type as Relapsing-Remitting (RRMS) or Primary-Progressive (PPMS) and; ii. completed the Edinburgh Handedness Inventory (EHI) were included in further analyses. Given that there was only one Secondary Progressive MS participant and four Clinically Isolated Syndrome participants (all women) these participants were not included in analyses. Additionally, participants who did not state their gender as female or male, did not answer all questions, as well as two individuals who had the exact same information and three individuals whose initial age at diagnosis fell more than two standard deviations below the mean (two individuals were diagnosed at 7.5 years old and one individual was diagnosed at 11 years old) were excluded from the analyses (Final N = 188; 158 women, 30 men).

Procedure

The research was approved by the Montclair State University Institutional Review Board and conducted in conformity with the Declaration of Helsinki. Advertisements containing a link to the survey on Qualtrics was posted to our laboratory's website and Facebook page, MS group online forums, MS group sites including the National MS Society, the National MS Society's Facebook pages and online MS magazine sites. Approval prior to posting was obtained via a site's administrator and registration to a site was completed when necessary. Advertisements on all sites were refreshed every two weeks on sites not requiring approval prior for posting and once every month on sites requiring approval. An excel file with links to all posted sites was created and updated for accuracy and organization.

After clicking on the link to the study within the advertisement, participants completed an anonymous informed consent form as well as demographic questions and questions about their MS diagnosis. Sequentially, participants completed The Patient Determined Disease Steps and the Edinburgh Handedness Inventory [3,5]. All questions were presented in the same order to participants, with demographic questions first, followed by questions regarding MS and handedness.

Edinburgh Handedness Inventory (EHI)

The EHI was used to examine three handedness classifications in efforts to replicate the handedness classifications used by Shirani, Cross and Naismith and Gardener, et al. Writing Hand was categorized as left or right using the question, "Which hand do you write with?" on the EHI, which was meant to be similar to the writing hand distinction made by Shirani, Cross and Naismith. Writing Hand ("always" writing with right hand (Wrh) versus any other selection of writing hand (scoring anything below +10) (Wlh)) [2]. Handedness Direction was defined as Left or Right based on scoring 0 and below or scoring +5, or above respectively. This categorization was meant to be similar to the eft-right distinction made by Gardener, et al. Third, Handedness Consistency was categorized as consistently right-handed versus consistently left-handed versus inconsistent. Handedness Consistency (Consistently RH (CRH) versus Consistently LH (CLH) versus Inconsistent (ICH)) was defined as scoring -80 and below signifying CLH, while +80 and above was CRH. ICH was defined as scoring between -75 and +75. This categorization was meant to be similar to the left-right-ambidextrous distinction made by Gardener, et al. These cut offs for determining the direction and degree of handedness were chosen based on the median of our sample, 80, which is equivalent to performing at least one of

ten activities with the non-dominant hand.

Patient Determined Disease Steps (PDD)

To assess disability in MS, the Patient Determined Disease Steps (PDD) was used. The following is the PDD scale: 0 = Normal; 1 = Mild Disability; 2 = Moderate disability; 3 = Early use of cane; 4 = Cane dependent; 5 = Bilateral support; 6 = Confined to wheelchair; and U = Unclassifiable [5].

Current Age

Participants were asked to state their age at the time of completing the survey.

Age at Diagnosis

Participants were asked to state when they were initially diagnosed by a doctor. Participants included the year and how long ago they were diagnosed, for example: February 2020, approximately two years ago. Using the participant's current age, age at diagnosis was calculated. First, current age was converted into months. Second, the participant's answer to "how many years ago" they were diagnosed was converted into months. Third, the number of "how many months ago" they were diagnosed was subtracted from their current age and divided by twelve.

Data Analysis

Analyses examined MS Type (RRMS vs. PPMS), Current Age, Age at Diagnosis and PDD Score, as a function of each of the Handedness Categorizations (Writing Hand, Handedness Direction, Handedness Degree). MS Type as a function of Handedness Categorization was examined using a Chi-square Test and Fisher's Exact Test. Current Age, Age at Diagnosis and PDD Score were examined using Independent Samples T-Tests and Analysis of Variance (ANOVA). Analyses were also conducted comparing men and women on MS Type, Current Age, Age at Diagnosis, EHI score and PDD Score. Women were also examined independently to determine if MS-Handedness relationships occur as a function of Gender, as per Gardener, et al., which also examined women only [1]. There were not enough men for independent analyses.

Results

There were 175 RRMS (151 women, 24 men) and 13 PPMS (7 women, 6 men). Chi-square tests were conducted to examine the relationship between MS Type and Handedness Classification (Wrh vs. Wlh, RH vs. LH and CLH vs. CRH vs. ICH). A significant result was observed between MS type and Writing Hand ($X^2(1, 188) = 5.13$, $p = 0.02$, Fisher's exact test ($p = 0.046$)). Wlh participants were more likely to be diagnosed with PPMS than were Wrh participants. Table 1 for MS Type distribution as a function of Handedness Classification.

Independent samples t-tests were performed examining Current Age, Age at Diagnosis and PDD score by Writing Hand and Handedness Direction, while an ANOVA was conducted for Handedness Degree. There were no significant effects ($p > .05$ for all comparisons (Table 2).

MS type, Current Age, Age at Diagnosis, EHI score and PDD score were examined as a function of gender. A significant result was observed between Gender and MS Type ($X^2(1, 188) = 9.50$, $p = 0.002$, Fisher's Exact test ($p = 0.008$)), indicating men and women were more likely to be diagnosed with RRMS than with PPMS. Table 3 for number of men and women as a function of MS Type. Independent samples t-tests were performed to examine Current Age, Age at Diagnosis, EHI score and PDD score in men and women. No significant effects were observed ($p > .05$ for all comparisons, Table 4.)

Chi-square tests were performed to examine the relationship between MS type and each Handedness Classification in women only ($n = 158$). Significant results were observed between MS type and Writing Hand ($X^2(1, 146) = 13.66$, $p = 0.000$, Fisher's exact test, $p = 0.005$). Wlh women were more likely to be diagnosed with PPMS than were Wrh women. Significant effects were also observed between MS type and Handedness Direction, $X^2(1, 158) = 7.18$, $p = 0.007$, Fisher's exact test $p = 0.033$). LH women were more likely to be diagnosed with PPMS than were RH women. Table 5 for distribution of MS Type as a function of Handedness Classification in women. No other effects were significant in any analyses (Table 6).

	Writing Hand *		Handedness Direction		Handedness Consistency		
	Always Right	Always Left	Right	Left	Consistently Right	Consistently Left	Inconsistent
PPMS	9 (5.84%)	4 (20%)	10 (5.92%)	3 (15.79%)	6 (46.15%)	1 (7.69%)	6 (46.15%)
RRMS	145 (94.16%)	16 (60%)	159 (94.08%)	16 (84.21%)	110 (62.86%)	6 (3.43%)	59 (33.71%)
*$p < 0.05$							

Table 1: Observed (%) N of MS type as a function of handedness classification collapsed by gender.

	Writing Hand			Handedness Direction			Handedness Consistency			
	Always Right	Always Left	Cohen's D	Right	Left	Cohen's D	Right	Left	Inconsistent	Eta Squared
N	154	20		169	19		116	7	65	
Current Age	48.50 (13.59)	51.38 (13.09)	0.22	48.72 (13.43)	51.74 (14.29)	0.22	50.01 (13.63)	58.86 (14.23)	47.15 (13.18)	0.03
Age at Diagnosis	36.26 (10.36)	37.32 (11.48)	0.1	36.25 (10.42)	38.19 (11.73)	0.17	37.33 (10.63)	40.43 (12.12)	34.77 (10.25)	0.02
PDD Score	3.07 (2.12)	3.18 (2.02)	0.05	3.09 (2.05)	3.05 (2.55)	0.02	3.15 (2.16)	4.14 (3.02)	2.98 (2.00)	0.01

Table 2: N and Mean (sd) of current age, age at diagnosis and PDD score as a function of handedness classification collapsed by gender.

	Gender **	
	Men	Women
PPMS	6 (20%)	7 (4.43%)
RRMS	24 (80%)	151 (95.57%)
**$p < 0.01$		

Table 3: Observed (%) N of gender as a function of MS type.

	Women	Men	Cohen's D
N	158	30	
Current Age	48.78 (13.78)	50.3 (12.09)	0.12
Age at Diagnosis	36.65 (10.61)	35.38 (10.33)	0.12
PDD Score	3.02 (2.10)	3.47 (2.13)	0.21
EHI Score	66.33 (50.10)	74.50 (36.47)	0.19

Table 4: N and Mean (sd) of current age, age at diagnosis, PDD score and EHI score as a function of gender.

	Writing Hand **		Handedness Direction *		Handedness Consistency		
	Always Right	Always Left	Right	Left	Right	Left	Inconsistent
PPMS	3 (2.34%)	4 (22.22%)	4 (2.86%)	3 (16.67%)	2 (28.57%)	1 (14.29%)	4 (57.14%)
RRMS	125 (97.66%)	14 (77.78%)	136 (97.14%)	15 (83.33%)	94 (62.25%)	6 (3.97%)	51 (33.77%)
*$p < 0.05$; **$p < 0.01$							

Table 5: Observed (%) N of MS type as a function of handedness classification in women.

	Writing Hand			Handedness Direction			Handedness Consistency			
	Always Right	Always Left	Cohen's D	Right	Left	Cohen's D	Consistently Right	Consistently Left	Inconsistent	Eta Squared
N	128	18		140	18		96	7	55	
Current Age	48.13 (13.89)	53.72 (12.35)	0.43	48.34 (13.67)	52.17 (14.58)	0.27	49.15 (13.75)	58.86 (14.23)	46.85 (13.42)	0.03
Age at Diagnosis	36.36 (10.33)	40.85 (10.81)	0.42	36.42 (10.44)	38.43 (12.02)	0.18	36.90 (10.65)	40.43 (12.12)	34.47 (10.46)	0.02
PDD Score	2.97 (2.10)	3.00 (2.43)	0.01	3.00 (2.04)	3.17 (2.57)	0.07	3 (2.05)	4.14 (3.02)	2.91 (2.04)	0.01

Table 6: N and Mean (sd) of current age, age at diagnosis and PDD score as a function of handedness classification in women.

Discussion

Generally speaking, the MS sample was representative of the MS population, with 158 women (84.04%) and 30 men (15.96%) which is comparable to larger MS populations with the gender ratio of 4:1 [6]. Furthermore, the ratio of MS types (RRMS: 93.09% and PPMS: 6.91%) in our sample was also representative in comparison to larger MS populations, where RRMS accounts for approximately 89% of MS-diagnosed patients [7]. Given that our sample is representative, it is reasonable to use our sample to investigate the relationship between MS type and handedness.

Participants who always write with their left hand were more likely to be diagnosed with PPMS than participants who always write with their right hand. This finding contradicts Shirani, Cross and Naismith, who found no association between writing hand and MS. Interestingly, in the examination of women only, left-handed women were more likely to be diagnosed with PPMS than were right-handed women. In brief, the current results suggest a possible association between handedness and MS type, but only in women.

This study extends the handedness measures used by Shirani, Cross and Naismith who measured handedness using Writing Hand, as well as Gardener et al., who used a self-assessment of handedness (LH vs RH) [1,2]. However, the current study also includes another Handedness Classification, Handedness Consistency, to measure participants' handedness based on degree (CLH vs CRH vs Inconsistent). In addition to extending handedness measures, the current study also tested both men and women with clinically diagnosed MS. Our results align with the findings of Gardener et al., study in that we find a greater severity of MS in left-handed women compared to right-handed women [1].

One reason why the current study may have found an effect of writing hand on MS type may be because of the quantitative nature of the handedness definition used here. Specifically, a: other work shows that handedness actually impacts recall for which hand is used during tasks, with the handedness groups differing in the accuracy of their recall for which hand they use and b: non-right-handers tend to be less strongly handed generally than are right-handers [8]. Therefore, it is very likely that participants in Shirani, Cross and Naismith's study, who reported writing with their left-hand were not as consistently left-handed as those participants classified as left-handed here [2].

Genetic explanations and environmental models have been proposed to explain the association between handedness and autoimmune diseases, such as MS. Crespi, Read and Hurd found that handedness and atopic diseases are genetically linked [9]. In their study they observed that there is a significant association of allelic variation in SETDB2 SNP rs4942830 with human handedness measured on a continuum from strong left to strong right. Their findings establish that there is in fact a 'handedness gene' that corroborates the idea that handedness is a continuum that is genetically related to some form of immune system function. The current study examined handedness on a continuum, through three handedness categorizations, in individuals with MS. The current results indicate that there is a link between non-right-handedness and severity of MS. Therefore, given the findings of Crespi, Read and Hurd, it is logical to presume that in the current study, MS is genetically linked to handedness [9].

Other proposals used to explain the link between immune system dysfunction and handedness include environmental influences, for example that of Geschwind, Behan and Galaburda (GBG) [10]. The GBG theory states that in-utero levels of testosterone influence cerebral and immune system developments [11-13]. According to this theory, there are two factors

particularly important for explaining the link between handedness and autoimmune disease. First, the increase in alteration of in-utero testosterone levels inhibits the development of the left hemisphere while allowing for greater growth of the right hemisphere, thus increasing the incidence of left-handedness. Second, the alterations in levels of testosterone during developmental stages in-utero is thought to have adverse effects on the thymus gland which is a main component in immune system response. Due to high levels of testosterone exposure in-utero, the thymus gland begins to deteriorate, thus increasing the chance of an autoimmune disease [14]. To summarize then, high exposure or sensitivity to testosterone in-utero may be linked to autoimmune diseases, such as MS and incidence of left handedness.

The GBG theory supports findings that left-handedness is associated with autoimmune disorders, though the model has received controversial debate in its validity [8,14,15]. The current findings do support the GBG theory in the sense that non-right-handed individuals are more likely to be diagnosed with PPMS a more severe type of MS compared to RRMS. Thus, it is plausible that individuals diagnosed with MS were exposed to high levels of testosterone in-utero which affected the development of their left hemisphere and thymus gland. In sum, the current study supports a possible link to altered in-utero testosterone levels causing an increase in autoimmune disorders such as MS and left-handedness.

There were several limitations here. First, because this was an online-based study, there is no guarantee that all self-reported answers are accurate. Second, the study had a small sample of self-reported clinically diagnosed MS patients with an unequal distribution size of men and women. However, this result supports the representativeness of the current sample.

Conclusion

In sum, the current study does find an association between handedness and MS type. Future research should examine larger MS samples, using in-person assessments. Although Shirani, Cross and Naismith did not find an association between MS and handedness, the current study provides results that there in fact may be a relationship between handedness and MS.

Data Availability

The authors confirm that the data that supports the findings of this study are available from the corresponding author, MV, upon reasonable request.

Conflict of Interests

The authors have no conflict of interest to declare.

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