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Frequency of Multiple Sclerosis as a Function of Handedness

Melissa Villafana

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Abstract

Background: Previous studies have examined the association between handedness and various autoimmune disorders. There is a possible link between handedness and immune system response due to high levels of testosterone in-utero which has been theorized to affect cerebral and immune system developments. To our knowledge, only two studies have examined the relationship between Multiple Sclerosis (MS) and handedness. Both studies used different measures of handedness and therefore, had contrasting results. In the current study, we suggest the need for a more appropriate way to measure handedness. **Objective:** This study investigates the relationship between MS type and Handedness. **Methods:** Participants with self-reported clinically definite MS were recruited online via the internet and social media sites relevant to the MS community. Participants completed several questionnaires about their MS diagnosis and hand preference. Only data from Primary Progressive MS (PPMS) and Relapsing Remitting MS (RRMS) participants (N = 188) were analyzed using three handedness classifications: Writing Hand, Handedness Direction, and Handedness Consistency. **Results:** A significant effect was observed between MS Type and Writing Hand as well as MS Type and Handedness Direction. **Conclusions:** The results suggest a possible association between handedness and MS type. Future research should examine larger MS samples with appropriate measures of handedness such as the current study's method.

Keywords: Multiple Sclerosis, Handedness, Autoimmune Disorder

MONTCLAIR STATE UNIVERSITY

Frequency of Multiple Sclerosis as a Function of Handedness

By

Melissa Villafana

A Master's Thesis Submitted to the Faculty of

Montclair State University

In Partial Fulfillment of the Requirements

For the Degree of

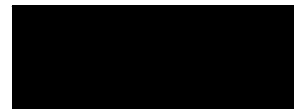
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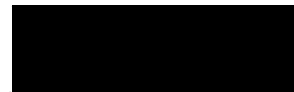
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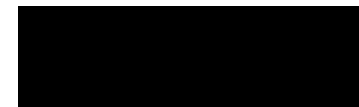
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FREQUENCY OF MULTIPLE SCLEROSIS
AS A FUNCTION OF HANDEDNESS

A THESIS

Submitted in Partial Fulfillment of the Requirements
For the Degree of Master of Arts

By

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Montclair, NJ

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Past studies have reported an association between handedness and autoimmune disease. Specifically, left-handedness is found to be associated with autoimmune disease. Autoimmune diseases can be defined as diseases in which the immune response results in damage of its own cells and tissues (Ngo et al., 2014). The damage of cells and tissues lead to targeted self-directed immune response, therefore causing the body to attack itself. Autoimmune diseases can either be systemic, such as systemic lupus erythematosus or affect specific organs, such as rheumatoid arthritis or multiple sclerosis (Ngo et al., 2014). Geschwind, Galaburda, and Behan (GBG) theorized that in-utero levels of testosterone influence cerebral and immune system developments (Geschwind & Behan, 1982; Geschwind & Galaburda, 1984; Geschwind & Galaburda, 1985). 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 (Geschwind & Behan, 1982; Geschwind & Galaburda, 1985). The increase in left-handedness is due to the right hemisphere taking over functions typically done by the left hemisphere, such as hand preference (McKeever & Riche, 1990). 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 (Geschwind & Behan, 1982; Geschwind & Galaburda, 1984; Geschwind & Galaburda, 1985). Due to high levels of testosterone exposure in utero, the thymus gland begins to deteriorate. This deterioration of the thymus gland decreases the body's ability to differentiate between self and foreign invaders, thus increasing the chance of an autoimmune disease (Morfit & Weekes, 2001). In other words, the GBG theory's central idea was that the processes that influence lateralization also affect the immune system (Bryden,

et al., 2005). To summarize then, high exposure or sensitivity to testosterone in-utero is linked to autoimmune diseases and incidence of left handedness.

The GBG theory has undergone critical analysis for its strengths and weaknesses. As previously mentioned, this model theorizes that high exposure or sensitivity to in-utero levels of testosterone influence both cerebral and immune system developments. Thus, this inhibits the development of the left hemisphere while allowing for greater growth of the right hemisphere. Furthermore, the GBG theory is able to identify the link between cerebral lateralization and immune system function by stating that testosterone during developmental stages breaks down the thymus gland, leading to increased incidence of autoimmune diseases (Morfit & Weekes, 2001). Despite its influential stance in the scientific community, it is beneficial to also identify its weaknesses. The greatest weakness of the theory is that its definition of anomalous dominance is too broad and warrants further clarification. Part of the GBG model explains that higher levels of testosterone also result in *anomalous dominance*, deviations in standard distributions of cerebral functions (Morfit & Weekes, 2001). Anomalous dominance is referred to as any deviation from normal division (Simon & Sussman, 1987). In an evaluation of the GBG theory, Bryden, McManus & Bulman-Fleming (1994) state that the definition of anomalous dominance leaves open to question what should be considered as “anomalous” (ie., to what degree are minor indications of left-handedness, right-hemisphere language, etc. indicative of an anomalous state?). Given the broadness of the definition, researchers can classify anomalous dominance in different ways, causing inconsistent support for the model (Morfit & Weekes, 2001). Additionally, McManus & Bryden (1991) discuss that the model also fails to account for general illness symptoms and infectious diseases. Autoimmunity varies between handedness groups and thus, an important missing explanation in the theory is the how general immune

function differs between right- and left-handers (Morfit & Weekes, 2001). The following paragraphs discuss studies that both support and do not support the GBG theory.

Since the proposal of the GBG theory, researchers have sought to examine the association of left-handedness and various autoimmune disorders. Geschwind and Behan (1982) investigated the frequency of individuals with immune disease, migraines, and developmental learning disorders and left-handedness in two separate experiments. Geschwind and Behan compared strongly left-handed and strongly right-handed individuals using a modified version of the Edinburgh Handedness Inventory to assess handedness. In the first experiment, they found higher frequencies of immune disease in left-handers compared to right-handers in the following reported immune disorders: coeliac disease, dermatomyositis, Hashimoto's thyroiditis, Crohn's disease, rheumatoid arthritis, thyrotoxicosis, ulcerative colitis, and uveitis (Geschwind & Behan, 1982). In the second experiment, they found higher frequencies of left-handed patients with migraines and myasthenia gravis – an autoimmune disease resulting in weakening of muscles (Geschwind & Behan, 1982).

A study conducted by Searleman and Fugagli (1986) tested the GBG theory in subjects with either Type I or Type II diabetes, Crohn's disease, or ulcerative colitis. Participants filled out a questionnaire that included questions about their specific disease, demographics, family handedness patterns, and hand preference using a seven-item index in which subjects rated their hand preference on multiple manual activities. Of the total sample, there were 279 control subjects, 119 Type I diabetics, 104 Type II diabetics, 152 subjects with Crohn's disease, and 46 subjects with ulcerative colitis. Their findings were consistent with the GBG theory; there was a significantly higher incidence of left-handed individuals with either Crohn's disease or ulcerative colitis (Searleman & Fugagli, 1986). Using a 1-tailed test, there was a significant difference

between left-handed Type I diabetics and Type II diabetics, however, when compared to their same-sex control counterparts, there was no significant difference in incidence for Type I and Type II diabetic males or females. Furthermore, a meta-analysis on autoimmune disease and handedness supports a statistically significant 13% increase in relative risk for autoimmune disorders such as asthma and ulcerative colitis, among left-handed individuals (Bryden et al., 1994). In brief, there have been studies supporting the relationship between left-handedness and autoimmune disease.

Other studies conducted in response to the GBG theory did not support the model. A study conducted by McKeever & Rich (1990) tested the theory in a sample of 3080 college students by administering an Immune Disorders Questionnaire (IDQ) and the Edinburgh Handedness Inventory (EHI). The IDQ listed various disorders: allergies, asthma, hay fever, eczema, urticaria, Crohn's Disease, ulcerative colitis, thyroid disorder, migraine, celiac disease, Addison's Disease, myasthenia gravis, rheumatoid arthritis, and Type 1 diabetes. For each disorder, students were directed to indicate on a four-point scale whether (1) had no reason to believe they had this particular disorder; to (4) had been diagnosed and treated by a physician. In females, the distribution of responses on the scale categories did not differ between left- and right-handers. Among males, no handedness effects were observed across any of the four scale categories. Overall, results provided no real support for the GBG theory.

A study conducted by Bishop (1986) used data from the National Child Development Study (NCDS) to examine the relationship between handedness, measured at 11, and allergy, eczema, asthma, psoriasis, Type I diabetes, and migraines. The NCDS is a longitudinal study conducted on British children born in the week of the 3rd to 9th of March 1958 and who were studied at birth, with follow-up assessments at 7 years, 11 years, and 16 years of age (Bishop,

1986). Handedness was assessed by various means in the NCDS, however, it was not possible to calculate a Laterality Quotient from the hand preference data since preference was recorded for only a handful of tasks (Bishop, 1986). The study reported no evidence that allergy, eczema, asthma, or psoriasis was related to handedness for either male or female children (migraine incidence was too low to provide a meaningful test). Furthermore, for Type I diabetes, the sample size was too low (9 females, 10 males) but there was a trend approaching significance ($p = 0.06$) for left-handedness to be more frequent in boys with diabetes compared to girls with diabetes (Bishop, 1986). Although there are studies that do not support the GBG theory, some have used a sample of undergraduate students. Although there are fairly equivocal findings for the link of handedness and autoimmune disorders, there still may be a link between handedness and autoimmune disorders, specifically MS, that can be accounted for.

Multiple Sclerosis (MS) has immunological and pathological features consistent with classification as an autoimmune disease. The etiology is unknown, however MS results in destruction of T-cells, consistent with other autoimmune diseases, such as rheumatoid arthritis (Ngo et al., 2014). T-cells are an essential part of the immune system and help protect the body. Dobson and Giovannoni (2019) have stated that MS has been previously classified as an organ-specific T-cell autoimmune disease. Therefore, the immunological abnormalities such as T-cell destruction in MS is autoimmune disease formation (Wootla et al., 2012). Furthermore, genetic susceptibility, specifically sex hormones, as well as environmental triggers, are pathological features that can also characterize MS as an autoimmune disease (Dobson & Giovannoni, 2019; Ngo et al., 2014). When these pathological features are combined, they play significant roles in the causal pathways that result in MS development, hence through T-cell destruction (Dobson & Giovannoni, 2019).

Additionally, Geschwind and Galaburda (1984) suggested that there is a potential relationship between sex hormones (i.e., testosterone) and the risk of MS due to their roles in the regulation of immune response. Testosterone has suppressive effects on the thymus gland, and therefore maturation of the immune system is likely to be affected increasing the risk of autoimmune disorders, such as MS (Geschwind & Behan, 1982). Ngo et al. (2014) also discussed sex hormones such as testosterone to be a possible mechanism for autoimmune diseases. Furthermore, Dobson and Giovanni (2019) indicate that the risk of MS may start in utero with sex steroid exposure, and progress through life with environmental exposures. Environmental factors might include low-levels of vitamin D, smoking, childhood obesity, and the Epstein-Barr virus (Ngo et al., 2014). In brief, MS has immunological and pathological features that can characterize it as an autoimmune disease as well as support a link to testosterone levels.

The thymus gland plays an important role in the formation of MS. Various studies have shown changes in the concentration and activity of T-lymphocytes (i.e., T-cells) in the thymus gland of patients with MS (D'Andrea et al., 1989). For example, Zaffaroni et al. (1984) used indirect immunofluorescence with specific monoclonal antibodies to demonstrate changes in the various blood T-lymphocytes subsets in different stages of the MS. In remission periods of MS, they reported an increase in T-lymphocytes, while in chronic-progressive periods of MS, they reported a decrease in T-lymphocytes (Zaffaroni et al., 1984). Their results confirm that MS patients show an alteration of T-lymphocytes as in other autoimmune diseases (Zaffaroni et al., 1984). Generally speaking, a decrease of T-lymphocytes, such as T-cells, in the thymus gland may predispose people to autoimmune diseases, such as MS. Therefore, the deficit of T-cells in MS patients may lend an explanation to the role of the thymus gland in the GBG theory. The

GBG theory states that exposure to high levels of testosterone in-utero can cause the thymus gland to deteriorate. Hence, high levels of testosterone in-utero can suppress the thymus gland and result in a weak maturation of the immune system, contributing to autoimmunity, such as MS.

MS is a disease in which the myelinated axons are destroyed in the central nervous system. The course of MS is unpredictable; however, it has been shown to cause initial episodes of reversible neurological deficits followed by progressive neurological deterioration (Goldenberg, 2012). MS is diagnosed on the basis of clinical findings and supporting evidence from magnetic resonance imaging (MRI) of the brain and investigation of the cerebral spinal fluid (Goldenberg, 2012). There are four main subtypes of MS: Relapsing-Remitting MS, Secondary Progressive MS, Primary Progressive MS and Clinically Isolated Syndrome. Relapsing-Remitting MS is noted by relapses of symptoms followed by periods of remission. Secondary Progressive MS is marked by continuous worsening of symptoms with or without periods of remission, whereas Primary Progressive MS is marked by continuous worsening of symptoms gradually from the start with no remissions. Clinically Isolated Syndrome is a rare form, marked by progression of symptoms from the beginning with intermittent flare-ups of worsening symptoms and no periods of remission (Hauser & Goodin, 2005).

Generally speaking, Primary Progressive MS is more severe than Relapsing Remitting MS. Primary Progressive MS is a chronic progressive subtype of MS and Relapsing Remitting MS includes remission periods (Goldenberg, 2012). As mentioned prior, part of the GBG theory centralizes that lateralization can affect the immune system (Bryden et al., 2005). Given this idea, there is a possibility that handedness impacts severity, and so there may be an affect of MS

subtype. It may be that patients with Primary Progressive MS are more likely to be left-handed compared to Relapsing Remitting MS patients.

As previously mentioned, there is a possible link between handedness and immune system response due to high levels of testosterone in-utero affecting cerebral and immune system developments. Therefore, it is appropriate to investigate the relationship between individual handedness differences and MS. To our knowledge, only two studies have investigated the relationship between MS and handedness. The first study conducted by Gardener et al. (2009) examined the association of left-handedness with MS in 121,701 female nurses in the United States with follow-ups from 1976 to 2002. Participants were taken from the ongoing Nurse's Health Study (NHS). Gardener and colleagues did not disclose the reason for only examining female nurses and not male nurses, though they discuss this as a limitation in their discussion. The nurses were asked to self-report natural hand preference from four choices: right, left, ambidextrous, or forced to change. Anyone who reported being ambidextrous or both naturally left and right handed were coded as ambidextrous. Those who reported being left handed and those who reported being forced to change, were coded as left handed. Similarly, those who reported being naturally right handed, excluding those who were ambidextrous, were coded as right handed. During follow-up with patients from 1976 to 2002, 210 cases with MS were confirmed and a 62% increase in relative risk of MS was observed among naturally left-handed women compared to naturally right-handed women. The results remained constant regardless of whether those who were forced to change handedness were excluded from the left-handed group, showing that the association is specific to only naturally left-handed individuals.

The second study was conducted by Shirani et al. (2019) which investigated the relationship between MS and handedness using clinically diagnosed MS patients. Data was used

from the Multiple Sclerosis Partners Advancing Technology Health Solutions network (MS PATHS). From a sample of 9,618 individuals diagnosed with MS, handedness data was only available for 8,888 patients. Handedness data in the MS PATHS was collected by asking the patients which hand they write with (Shirani et al., 2019). Subjects self-reported either left-handed (LH) or right-handed (RH) preference. Of the 8,888 patients, 917 (10.3%) were LH. Results indicated no strong evidence to suggest that left-handed MS patients may have an earlier MS onset. Also, the mean age for MS onset was only slightly higher in LH patients compared to RH patients ($p=0.066$). Overall, Shirani et al. (2019) did not observe any evidence to suggest a relationship between individual differences in handedness and MS.

The two studies examining MS and handedness differed in their findings, participants, and measures/definitions of handedness. Gardener et al. (2009) found that left-handed women may be more likely to have MS than right-handed women, and Shirani et al. (2019) found that left-handedness is not associated with MS. These different findings can be attributed to dissimilarities in their samples and measures of handedness. For example, Gardener et al. (2009) only examined a sample of women while Shirani et al. (2019) examined both men and women. This is important because effects of testosterone on lateralization is reported to differ between men and women (Grimshaw et al., 1995) and it is unclear how gender differences might interact with handedness and MS relationships. A study conducted by Grimshaw et al. (1995) examined in-utero testosterone levels in second trimester amniotic fluid and lateralization of speech, affect, and handedness at age 10. Their results indicated that females with higher in-utero testosterone levels were more strongly right-handed compared to males (Grimshaw et al., 1995). The third difference is found in their measures/definitions of handedness. Gardener et al. (2009) measured handedness using one question in which participants self-reported their natural hand preference

from four choices (left, right, ambidextrous or forced to change). Although the study may in fact measure some form of degree of handedness using the choice 'ambidextrous', it is not clear that by asking this one question the researchers are getting enough information about the participants' handedness to determine their hand preference. For example, other research (Isaacs et al., 2006; Searleman & Fugagli, 1986) has indicated that hand use preference varies on a continuum across many activities, and cannot be determined via answers to a single question. Furthermore, it is uncertain how the participants conceptualize their answer to this question and therefore, this is not an accurate form to measure handedness. Shirani et al. (2019) measured left- vs. right-handers on the basis of which hand the participants reported writing with (right- vs. left-hand). Although in this study, the question does operationally define handedness, it is not an appropriate measure of handedness. According to other literature, sometimes individuals may write with their right hand but given other information they may provide across other activities, they may not be right-handed (Prichard et al., 2013). Although asking participants which hand they write with is a better measure of handedness than Gardener et al.'s (2009) measure of handedness, it is not supported in the literature as a clear method to determine handedness.

It is plausible that the difference in handedness measures are a reason for the contrasting results of the studies. For this reason, a better way to measure handedness is to use a validated instrument, such as the Edinburgh Handedness Inventory (EHI; Oldfield, 1971) that has been used across several studies that seems to more appropriately measure handedness.

Historically, handedness studies have focused on left-handers vs. right-handers and have found conflicting results (Prichard et al., 2013). Over recent years, there has been extensive evidence demonstrating that investigating handedness on the basis of left- vs. right-handedness is not an appropriate method of measurement (Prichard et al., 2013). Past research examining

individual differences in handedness has focused on the *direction* of hand preference (LH vs. RH) (Prichard et al., 2013). A more appropriate way to investigate handedness is comparing consistent- and inconsistent-handers. Consistent handedness (CH) can be defined as using the dominant hand for all common manual activities, and inconsistent handedness (ICH) as using the non-dominant hand for at least one common manual activity (Prichard et al., 2013). Therefore, how consistently an individual prefers to use one hand over the other in a variety of tasks is a more specific way to determine handedness. To summarize, here we argue that the reason why Gardener et al. (2009) and Shirani et al. (2019) have found inconsistent results is because the measure used to define handedness has normally been the *direction* of handedness. Though this has been the case for majority of past studies, Gardener et al. (2009) did measure some form of *degree* of handedness through the choice of ambidextrous as a hand preference which could be interpreted as inconsistent-handedness. Still, their handedness measure, as previously explained, did not accurately measure participants' handedness. By measuring *degree* of handedness in addition to *direction*, researchers may be able to see differences based on handedness.

The current study investigates the relationship between MS type and handedness using both *direction* and *degree* of hand preference as well as which hand people write with. To elaborate, in the current study, we first replicate the handedness measure used by Shirani et al. (2019) to look at writing hand. Second, we looked at handedness direction (LH vs. RH) using the EHI as typically scored to compare these groups. This will replicate the handedness measure used by Gardener et al. (2009). Third, we look at degree of handedness (CH vs. ICH) by using quantifiable measures of the EHI instead of only using one self-reported question as the previous two studies did. Individuals with self-reported clinically definite MS were recruited online via the internet and social media using sites specifically relevant to the MS community up to an

international level. The aim of the study was to determine whether there is an association between hand preference and self-reported, clinically definite MS types, Relapsing Remitting MS (RRMS) and Primary Progressive MS (PPMS).

Method

Participants

The research was approved by the Montclair State University Institutional Review Board and conducted in conformity with the Declaration of Helsinki (2013). Participants were required to be 18 years old or older, native English speakers, 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).

Materials and Procedure

After approval from the local Institutional Review Board, advertisements containing a link to the survey on Qualtrics were 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. Local, national and international MS sites were included for postings. Approval prior to posting was obtained via the site's administrator and registration to the site was completed when necessary. Advertisement 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 (PDD; Hohol et al., 1995), and the Edinburgh Handedness Inventory (Oldfield, 1971). 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). Handedness was measured using The Edinburgh Handedness Inventory (EHI). The inventory asks respondents to report which hand they prefer to use for ten manual activities (Oldfield, 1971). The EHI was used in the study because it enables a distinction between consistent- and inconsistent-handedness to be made. Total scores on the inventory range from -100 (consistent LH) to +100 (consistent RH) and were scored using typical scoring practices. The median in each study is used to classify the cut-off scores to determine the direction and degree of handedness. The median in our study was 80. We

examined three classifications of handedness, i. Writing Hand (always writing with right hand (Wrh) versus not always writing with right hand (Wlh)); ii. Handedness Direction (RH versus LH) and; iii. Handedness Consistency (consistently-handed (CH) versus inconsistently-handed (ICH)). Writing Hand and Handedness Direction were designed to replicate previous research handedness classifications using the EHI. First, handedness was categorized as left versus right based on Writing Hand using the question, “Which hand do you write with” on the EHI. Only individuals who stated they always wrote with their right hand were ‘right-handed’ (Wrh) and only individuals who stated they always wrote with their left hand were ‘left-handed’ (Wlh). Wrh participants scored +10 on the Writing Hand question and Wlh participants scored anything below. Second, handedness was also categorized as left versus right based on scoring 0 and below as left-handed versus scoring +5 and above as right-handed using the entire EHI. This categorization was meant to be similar to the left-right distinction made by Gardener et al. (2009). Third, handedness was also categorized as consistent versus inconsistent based on categorizing consistently-handed participants as those who scored -80 and below or +80 and above, and inconsistently-handed as participants who scored between -75 and +75 on the entire EHI. These cut offs 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 (Prichard et al., 2013). This was done because Handedness Consistency is a good conceptualization that past researchers have not looked at and previous work has suggested that the differences between handedness groups may vary on their *degree* of hand preference and not their *direction* of hand preference (Prichard et al., 2013).

Patient Determined Disease Steps (PDD). To assess disability in MS, the Patient Determined Disease Steps (PDD; Hohol et al., 1995) 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 (Hohol et al., 1995).

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 had to include the year and how long ago they were diagnosed, for example: February 2020, approximately two years ago. Using the participant's current age, we were able to calculate their age at diagnosis. First, we converted their current age into months. Second, we converted 'how many years ago' they were diagnosed into months. Third, we subtracted how many months ago they were diagnosed from their current age and divided that number by twelve.

Data Analysis

All main analyses examined three continuous dependent variables: Current Age, Age at Diagnosis, and PDD Score and one categorical dependent variable: MS Type, as a function of handedness categorization (Wrh vs Wlh, RH vs. LH, and CH vs ICH). Analyses were first conducted comparing men and women on MS Type, Current Age, Age at Diagnosis, EHI score, and PDD Score using Chi-squared Test, Fisher's Exact Test and Independent Samples T-tests. Next, men and women were collapsed and examined on four dependent variables – MS Type, Current Age, Age at Diagnosis, and PDD score – by Handedness Classification using Chi-squared Test, Fisher's Exact Test and Independent Samples T-tests. Lastly, women were examined separately by Handedness Classification to see if there are effects on MS type, Current

Age, Age at Diagnosis, and PDD score using Chi-squared Test, Fisher's Exact Test and Independent Samples T-tests.

Results

Of the 188 participants, 158 were women and 30 were men. There were 175 RRMS participants (151 women, 24 men) and 13 PPMS participants (7 women, 6 men). First gender was compared on MS type, Current Age, Age at Diagnosis, EHI score and PDD score. A chi-square test was performed to examine the relationship between gender and MS Type. A significant result was observed between gender and MS Type, $\chi^2(1, 188) = 9.50, p = 0.002$. Due to small observed frequencies, Fisher's exact test was used to determine if there was a significant effect between gender and MS Type. A significant association was observed, ($p = 0.008$).

Women were more likely to be diagnosed with RRMS than men. See table 1 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 effects were observed in any of the t-tests ($p > .05$ for all comparisons). See table 2 for means and standard deviations of Current Age, Age at Diagnosis, PDD score and EHI score compared by gender.

The next set of analyses looked at the sample as a whole, that is, collapsing by gender. A chi-square test was conducted to examine the relationship between MS Type and Handedness Classification (Wrh vs Wlh, RH vs. LH, and CH vs ICH). A significant result was observed between MS type and Writing Hand, $\chi^2(1, 188) = 5.13, p = 0.02$. As a result of small observed frequencies, Fisher's exact test was performed to examine the relationship between MS Type and Writing Hand. A significant association was observed, ($p = 0.046$). Wlh participants were more likely to be diagnosed with PPMS than Wrh participants. RH vs. LH and CH vs. ICH both resulted in no effects ($p > .05$ for all comparisons). See table 3 for MS Type distribution as a

function of Handedness Classification collapsed by gender. Independent samples t-tests were performed examining Current Age, Age at Diagnosis, and PDD score by Handedness Classification. All results showed no significant effects ($p > .05$ for all comparisons). See table 4 for means and standard deviations of Current Age, Age at Diagnosis, and PDD Score across Handedness Classification collapsed by gender. Therefore, the next set of analyses were conducted in women only.

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, $X^2(1, 146) = 13.66, p = 0.000$. Given the small observed frequencies, Fisher's exact test was performed and a significant association was observed between MS Type and Writing Hand, ($p = 0.005$). Wlh women were more likely to be diagnosed with PPMS than Wrh women. Significant effects were also observed between MS type and Handedness Direction, $X^2(1, 158) = 7.18, p = 0.007$. Using Fisher's exact test significant association was also observed between MS Type and Handedness Direction, ($p = 0.033$). LH women were more likely to be diagnosed with PPMS than RH women. Handedness Consistency did not reach statistical significance. See table 5 for distribution of MS Type as a function of Handedness Classification in women. Independent samples t-tests were conducted to compare Current Age, Age at Diagnosis, and PDD scores as a function of Handedness Classification. No effects were observed on all tests ($p > .05$ for all comparisons). See table 6 for means and standard deviations of Current Age, Age at Diagnosis, and PDD Score as a function of Handedness Classification in women.

Discussion

In the current study, the relationship between MS and handedness was examined. Three continuous dependent variables (Current Age, Age at Diagnosis, and PDD Score) and one categorical dependent variable (MS type) were examined using three Handedness Classifications (Writing Hand, Handedness Direction, and Handedness Consistency). Significant effects were observed between MS Type and Writing Hand as well as Handedness Direction using chi-square and Fisher's exact tests. A significant effect was observed between MS Type and Writing Hand such that 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. Additionally, in the examination of women only, left-handed women were more likely to be diagnosed with PPMS than right-handed women. In brief, these significant effects suggest a possible association between handedness and MS type.

Generally speaking, the MS sample was representative of the MS population. Our sample consisted of 158 women (84.04%) and 30 men (15.96%). Compared to larger MS populations, our sample aligns with the gender ratio of 4:1 (Harbo et al., 2013). 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 (Sumelhati et al., 2014). Furthermore, despite the fact that there were no between group gender differences in our analyses collapsing by gender, other research makes it clear that men are more likely to be left-handed and have a greater incidence of MS severity (Gilbert & Wysocki, 1992; Harbo et al., 2013). Given that our sample aligns with the demographics of larger MS populations, it is reasonable to use our sample to investigate the relationship between MS type and handedness.

Overall, the results did support the hypothesis that there is an association between MS type and handedness. Although no effects were observed for Current Age, Age at Diagnosis, and PDD score, there was an effect between MS Type and Writing Hand in both women-only and the sample as a whole as well as MS Type and Handedness Direction in women only. Specifically, results here are similar to those found by Gardener et al. (2009). Although there seems to be an overall effect, it could be a function of the fact that there were many tests conducted, resulting in a type I error.

The current study was able to replicate and implement a more appropriate measure of handedness. This study used the same handedness measures as Shirani et al. (2019) who used Writing Hand as a single measure of handedness, and Gardener et al. (2009) who used Handedness Direction as a measure of handedness. However, the current study also includes a third Handedness Classification, Handedness Consistency, to measure participants' handedness based on degree. In the current study, Handedness Consistency did not result in any significant effects across our analyses. However, in the current study we observed effects in Writing Hand and Handedness Direction. The current results imply that measuring handedness direction may in fact be a valid measure of handedness. It is worth noting that although handedness direction had significant effects and handedness degree did not, together they can more appropriately conceptualize individual differences in handedness. Therefore, though Handedness Consistency did not result in any significant effects, it still offers a more appropriate conceptualization and measure of handedness for future researchers to implement in their handedness studies.

Furthermore, the current study builds on the methodology of both Gardener et al. (2009) and Shirani et al. (2019). To expand on the methodology of both studies, we tested both men and women with clinically diagnosed MS as well as offered more than one handedness measure to

more appropriately classify handedness. Gardener et al. (2009) found an increase in risk of MS among naturally left-handed women compared to naturally right-handed women, while Shirani et al. (2019) found no evidence to suggest an association between MS and handedness. Our results replicate the findings of Gardener et al.'s (2009) study in that we find a greater severity of MS in left-handed women compared to right-handed women.

One theoretical implication that attempts to explain the association between handedness and MS is the Geschwind, Behan, and Galaburda (GBG) theory. Geschwind, Galaburda, and Behan (GBG) theorized that in-utero levels of testosterone influence cerebral and immune system developments (Geschwind & Behan, 1982; Geschwind & Galaburda, 1984; Geschwind & Galaburda, 1985). Essentially, the theory explains that alteration of in-utero testosterone levels prohibits the development of the left hemisphere, thus allowing for greater growth of the right hemisphere, causing increased left-handedness. Also, the alteration in in-utero testosterone levels induces adverse effects on the thymus gland – an important part of immune system response. While in-utero, the immune system is also maturing (Geschwind, 1982). Therefore, during the periods of increased testosterone levels affecting the development of the left hemisphere, the immune system is likely to be affected causing the rise of autoimmune disorders later in life (Geschwind, 1982). The GBG theory supports findings that left-handedness is associated with autoimmune disorders, though the model has received controversial debate in its validity. 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. Overall, the current findings show a significant relationship between non-right-handedness and MS type. In

connection to the GBG theory, it is plausible that participants experienced high exposure or sensitivity to testosterone in-utero which affected the development of the left hemisphere causing left-handedness. 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.

Despite our study's aim, there were several limitations found. First, our study was online-based. Individuals with self-reported clinically definite MS were recruited via the internet and social media sites. Since this was an online-based study, there is no guarantee that all self-reported answers are accurate. Second, since participants completed the survey online, this poses self-selection bias on the study. Third, our study had a small sample of self-reported clinically diagnosed MS patients with an unequal distribution size of men and women. The reason we also kept men and women separate is due to individual gender differences in handedness and MS. Generally speaking, men tend to have more severe progression, may have an earlier onset age of MS, and tend to be more left-handed than women (Papadatou-Pastou et al. 2008; Shirani et al. 2019). Therefore, any effects we would see could be due not to handedness, but to these confounding variables. Data analyses were conducted to observe effects between our dependent variables and Handedness Classifications using chi-square tests, Fisher's exact tests and independent samples t-tests. To conclude, though there were limitations to the current study, it offers a preliminary insight into a more appropriate measure of handedness for future directions.

In sum, the current study does find an association between handedness and MS type. Future research should also examine larger MS samples with appropriate measures of handedness such as the current study's method. To elaborate, future research should examine both handedness direction and degree. Although there are only two other known studies

examining MS and handedness relationship, the current study provides a more accurate insight into findings using a more appropriate measure of handedness.

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Table 1*Observed (%) N of Gender as a Function of MS Type*

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

**** $p < 0.01$**

Table 2

N and Mean (sd) of Current Age, Age at Diagnosis, PDD Score, and EHI Score as a Function of Gender

	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 3

Observed (%) N of MS Type as a Function of Handedness Classification Collapsed by Gender

	Writing Hand *		Handedness Direction		Handedness Consistency	
	Always Right	Always Left	Right	Left	Consistent	Inconsistent
PPMS	9 (5.84%)	4 (20%)	10 (5.92%)	3 (15.79%)	7 (5.69%)	6 (9.23%)
RRMS	145 (94.16%)	16 (60%)	159 (94.08%)	16 (84.21%)	116 (94.31%)	59 (90.77%)

* $p < 0.05$

Table 4

N and Mean (sd) of Current Age, Age at Diagnosis and PDD Score 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	Consistent	Inconsistent	Cohen's D
N	154	20		169	19		123	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)	47.15 (13.18)	0.21
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)	34.77 (10.25)	0.25
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)	2.98 (2.00)	0.08

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	Right	Left	Consistent	Inconsistent
PPMS	3 (2.34%)	4 (22.22%)	4 (2.86%)	3 (16.67%)	3 (2.91%)	4 (7.27%)
RRMS	125 (97.66%)	14 (77.78%)	136 (97.14%)	15 (83.33%)	100 (97.09%)	51 (92.73%)

* $p < 0.05$ ** $p < 0.01$

Table 6

N and Mean (sd) of Current Age, Age at Diagnosis, and PDD Score as a Function of Handedness

Classification in Women

	Writing Hand			Handedness Direction			Handedness Consistency		
	Always Right	Always Left	Cohen's D	Right	Left	Cohen's D	Consistent	Inconsistent	Cohen's D
N	128	18		140	18		103	55	
Current Age	48.13 (13.89)	53.72 (12.35)	0.43	48.34 (13.67)	52.17 (14.58)	0.27	49.81 (13.93)	46.85 (13.42)	0.22
Age at Diagnosis	36.36 (10.33)	40.85 (10.81)	0.42	36.42 (10.44)	38.43 (12.02)	0.18	37.55 (10.63)	34.96 (10.45)	0.24
PDD Score	2.97 (2.10)	3.00 (2.43)	0.01	3.00 (2.04)	3.17 (2.57)	0.07	3.08 (2.13)	2.91 (2.04)	0.08