Longitudinal Variation of Depressive Symptoms in Multiple Sclerosis Patients in Relation to Temporal Lobe Lesion Volume

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1. Abstract

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Title of thesis: Longitudinal Variation of Depressive Symptoms in Multiple Sclerosis Patients in Relation to Temporal Lobe Lesion Volume

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The current thesis aimed to investigate whether there was an association between depressive symptoms and temporal lobe lesion volume in patients with multiple sclerosis (MS). Detailed data from 76 MS patients recruited from Oslo University Hospital was collected across four time points over the span of seven years. This included MRI scans, clinical information including the Expanded Disability Status Scale (EDSS), and self-reported Beck's Depression Inventory (BDI) questionnaires. This longitudinal data was assessed using linear mixed effect models in order to properly assess the relationship between BDI scores and variations in lesion volumes and brain volumes by using detailed information based on their MRI scans. The main results of the present study found no associations between BDI score and temporal lobe lesion or total brain volume. However, there was a noticeable, significant decline in multiple BDI question scores, as well as a continual low EDSS average across three time points, and a continual low BDI average across all four time points. In summary, our results indicate that while there is no apparent association between BDI score and lesion volume, there is a decline in temporal lobe and whole brain volume over time.

This study was an independent research project. All data used was collected by the Multiple Sclerosis Research group at the University of Oslo and Oslo University Hospital.

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Abbreviations

BBB – Blood brain barrier

BDI – Beck's Depression Inventory

CIS – Clinically isolated syndrome

CNS – Central nervous system

EDSS – Expanded Disability Status Scale

MDD – Major depressive disorder

MS – Multiple sclerosis

PPMS – Primary-progressive MS

RIS – Radiologically isolated syndrome

ROI – Region of Interest

RRMS – Relapsing-remitting multiple sclerosis

SPMS – Secondary-progressive multiple sclerosis

2. Introduction

2.1 A Brief Overview of Multiple Sclerosis

Multiple sclerosis (MS) is an incurable, chronic, immune-mediated inflammatory, demyelinating, and neurodegenerative disease of the central nervous system (CNS) with highly inconsistent ages of onset, disease progression, and symptom severity across patients (Brownlee et al., 2017; Faissner & Gold, 2019). Symptomology of MS is equally heterogenic and can present with mild to severe disturbances of visual processing, urinary and bowel functionality, cognitive processing, balance, and general sensation and mobility (Brownlee et al., 2017).

Due to the immense complexity of the disease, and kaleidoscopic factors leading to its onset, it is then imperative to observe the pathogenic role of the immune system; a core, critical, and consistent component present in every MS phenotype (Lucchinetti et al., 2000; Lubetzki & Stankoff, 2014; Trapp & Nave, 2008). According to Legroux and Arbour (2015), Mars et al. (2011), and Trapp and Nave (2008), atypically functioning immune cells, more specifically CD4 and CD8 T lymphocytes, are able to pass through and initiate a breakdown of the blood brain barrier (BBB), a restrictive barrier that typically protects the CNS from disease or injury stemming from pathological agents and toxins. It is the increased introduction of these lymphocytes, in response to increased activation of the immune system and proinflammatory cytokines, that significantly contribute to the initial inflammatory response, subsequent deterioration of myelin, and formation of lesions in MS (Kaskow & Baecher-Allan, 2018; Legroux & Arbour, 2015; Mars et al., 2011; & Spencer et al., 2017).

While the precise cause of MS is unknown, it is commonly agreed upon that both environmental and genetic factors contribute to the development and progression of the disease (Asherio & Munger, 2016; Goodin, 2016; & Goodin, 2014). In terms of environmental factors, one of the largest potential risk factors is vitamin D deficiency due to a lack of exposure to sunlight (Holick, 2004). This is frequently seen in geographical locations residing at higher latitudes, where there are, typically, more instances of MS compared to countries residing at lower latitudes with more tropical climates (Archeson & Bachrach, 1960; Ascherio & Munger, 2016; & Kurtkze, 1967). Notably, however, is that in Norway, a country which experiences extended

periods of reduced or no sun, there appear to be lower instances of MS in coastal communities that consume greater amounts of fish, compared to inland communities, which consumed, on average, a lesser amount of fish (Swank et al., 1952; Westlund, 1970). The significance of vitamin D in relation to MS remains a critical component of research, with several studies indicating not only the increased risk lower vitamin D levels play in the development of MS, but also its role in disability severity and rate of relapses. (Koven et al., 2013; Sintzel, Rametta, & Reder, 2017; & Smolders et al., 2008).

An additional and equally critical environmental factor that plays a role in the age of onset of MS is geographical latitude. In tandem with vitamin D deficiency, geographical locations at higher latitudes experience periods in which individuals have reduced exposure to sunlight. This is especially true in Scandinavian countries. Further, the role of latitude in MS is heavily supported in Tao et al. (2016), in which individuals of European descent living at higher latitudes had an age of onset 1.9 years earlier compared to those living at lower latitudes. In addition, individuals with greater sunlight exposure showed a greater age of onset compared to those with reduced sunlight exposure (Tao et al., 2016).

An intermediary bridge between environmental and genetic factors leading to the development of MS may be apparent in an infant's birth month. The notion of reduced vitamin D playing a role in the inception of MS, as stated in Holick (2004), and geographical location contributing to reduced sunlight exposure and earlier age of onset as stated in Tao et al. (2016), appears to apply to in utero development as well. According to Willer et al. (2004), a significantly larger number of infants born during May were later diagnosed with MS, compared to those born during November in Denmark, Sweden, Great Britain, and Canada, countries with higher latitudes and prolonged winter periods consisting of reduced to no sun. This then provides an extensive reaffirmation of the significance of vitamin D deficiency in the development and progression of MS, as well as the geographical latitude of birth.

The complexity of MS dramatically increases when observing the genetic components of the disease. Notably, individuals related to a family member with MS have an increased risk of developing the disease, with a 2-5% risk if the afflicted individual is a parent, sibling, or child; a 1-2% risk if the afflicted individual is an aunt or uncle; and a less than 1% chance if the afflicted

individual is a first cousin (Goodin, 2010). The true oddity of the disease lies with monozygotic twins, which appear to have the highest risk of developing MS at approximately 25% compared to dizygotic twins, which have an approximate 5% risk of developing MS (Goodin, 2010; Willer et al., 2003). While the risk is on par with siblings for dizygotic twins, and significantly greater for monozygotic twins, pinning the precise underlying genetic components in MS still remains difficult. Notably is the DRB1*1501 allele on the DRB1 locus. While this allele has a fairly strong association with MS, it appears that only a minor percentage of DRB1*1501 carriers ever go on to develop MS (Goodin, 2014; Goodin, 2012; Hafler et al., 2007). This may then suggest that while the genetic component plays a significant role, the development of MS is dependent on the alleles present as well as environmental factors.

Another important component in the development of MS is gender. A nationwide prevalence study of MS in Sweden revealed that the gender ration of patients with MS was 2.35 females to every male (Ahlgren et al., 2011). A similar statistic is reaffirmed in Ascherio and Munger (2016), which notes that the prevalence ratio of MS is between 1.5 and 2.5 females for every male. In terms of genetics, while additional risk alleles have been found, there have been no distinctively clear difference between male and female patients (Harbo et al., 2013).

It may then be possible to further understand why the prevalence of MS is significantly higher in territories located at higher latitudes. When accounting for genetic susceptibility beginning in utero fetal development during months with reduced sun exposure, in tandem with a higher likelihood of tobacco use, which according to Navas-acien (2018) is above 20% for men and 15% for women in most European countries, be it maternal, paternal, or performed by the at-risk individual, along with the presence of alleles, notably DRB1*1501, which are linked to the later development of MS, it becomes apparent that individuals located in these territories at higher latitudes have a plethora of environmental factors that may act upon genetic susceptibilities compared to those at lower latitudes where sun exposure is greater, and in territories with reduced tobacco usage.

2.2 Phenotypes of Multiple Sclerosis

The complexity of MS extends beyond the factors that cause its onset. Truly, in order to appropriately understand the disease, it is imperative to observe the different phenotypes of MS. Notably, clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), and primary progressive MS (PPMS) are all distinct variants of MS that should be understood before moving forward.

CIS is an important addition to the MS criterion. While CIS is not necessarily MS, it does represent the first potential presentation of the disease, with signs of early inflammatory demyelination becoming readily apparent (Lublin et al., 2014). Additionally, the importance of this categorization is reaffirmed in Miller et al. (2005), which found that 85% of patients that go on to develop MS first had an onset of CIS.

RRMS is the most common form of MS and constitutes approximately 85% of all MS patients (Goldenberg, 2012; Loma & Heyman, 2011). RRMS, characteristically, exhibits periods of symptomatic flare-ups or relapses followed by a remission period during which there is a reduction in symptoms or an absence of them entirely (Goldenberg 2012).

SPMS is often considered the secondary form of RRMS, with nearly 65% of RRMS patients going on to develop SPMS (Ghasemi et al., 2017). SPMS is a more severe form of MS, in that individuals experience greater neurological decline and a worsening of symptoms without any instances of plateauing or remission (Goldenberg, 2012).

Lastly is PPMS, a very severe form of MS that accounts for 10% of MS diagnoses. What makes PPMS more severe is not only its greater resistance against drugs used for treatment, but its continual worsening of symptoms beginning at disease onset. While it is true that there may be periods of plateauing, the lack of remissions periods is especially difficult for those afflicted with the disease (Goldenberg, 2012).

2.3 Current Methods of Diagnosis and Treatment in MS

Presently, the revised 2017 McDonald criteria (Thompson et al., 2018) are commonly used in the diagnosis of MS, with a categorization of evidence needed for a diagnosis. (1) A clinical episode in which symptoms are either reported by the patient, or the presence of inflammatory demyelination in the CNS that cannot be attributed to fever or infection; (2) a patient that has at least 2 clinical attacks and 1 lesion with dissemination in space, indicated by another clinical attack with a different CNS site association, or by using MRI (3) a patient that has 1 clinical attack and at least 2 lesions with dissemination in time indicated by another clinical attack, or CSF-specific oligoclonal bands; (4) a patient with 1 clinical attack and 1 lesion with dissemination in space, indicated by another clinical attack with a different CNS site association, or by using MRI and with dissemination in time indicated by another clinical attack, or CSF-specific oligoclonal bands (Thompson et al., 2018). It should be noted that, in addition, the use of brain and spinal MRI is recommended for patients in order to both confirm the MS diagnosis and to quash differential diagnoses (Dobson & Giovannoni, 2018).

Treatments for MS often involve drug therapy with several different options currently available including, but not limited to Interferon-β, Natalizumab, and immunosuppressants (Tavazzi, Rovaris, & La Mantia, 2014). Interferon-β is given in order to promote the production of anti-inflammatory cytokines and reduce the formation of novel lesions, Natalizumab aids in the prevention of lymphocytes from entering the CNS, and immunosuppressants such as Cyclophosphamide aid in the reduction of CNS inflammation (Tavazzi, Rovaris, & La Mantia, 2014). It is often typical that there is a combination of drug therapy and some form of physical therapy to aid with the physical symptoms of MS.

2.4 Depressive Symptoms in Subjects with MS

At a rate 3 to 10 times greater than the general population, and with an approximate 40% to 60% lifetime prevalence, major Depressive Disorder (MDD) afflicts approximately 15% – 30% of clinically diagnosed MS patients (Cane & Schwid, 2002; Pucak et al., 2007; Siegert & Abernethy, 2005; Skokou et al., 2012). With depression being more common in MS than other neurological disorders, the already impaired function and reduced quality of life in MS patients

is impacted further (Lobentanz, et al., 2004; Pucak, et al., 2007). It is then necessary and critical to understand this diagnostic criteria before delving further.

The criteria for MDD, according to the DSM-V, is the presence of five or more of the following symptoms (one of which being depressed mood or a loss of interest or pleasure) during the same two week period while also causing an impairment in typical functioning: (1) depressed mood for a majority of the day that is either self-identifiable with feelings of sadness or hopelessness, or identifiable by others; (2) a noticeable and self-identifiable decline in pleasure or interest in activities either a majority of the day or daily; (3) Significant weight loss or gain (5% change in body weight within a month) independent of intentional dieting; (4) frequent, nearly daily insomnia or hypersomnia; (5) retardation or agitation of psychomotor functionality that is observable by others and extends beyond restlessness or typically slowed responses; (6) near daily fatigue or loss of energy; (7) excessive or inappropriate feelings of potentially delusional guilt or worthlessness on a near daily basis; (8) near daily, and self or externally identifiable diminished concentration or ability to think, or indecisiveness; (9) recurring thoughts of death or planned or unplanned suicidal ideation, or an attempt at committing suicide. It should be noted further that these symptoms must not only cause clinically significant distress or impairment in daily functioning of the individual, but must also not be a result of foreign substances or other medical condition (American Psychiatric Association, 2017).

Another important tool in assessing the psychological status of the patient is BDI. This assessment serves as a self-report questionnaire that touches on the symptoms of MDD, including feelings of sadness, changes in interest or energy, or changes in the ability to concentrate (Beck et al., 1996). Further, the diagnostic capabilities of BDI have been assessed and found to be significant in numerous studies (Park et al., 2020; Garcia-Batista et al., 2018; & Fischer et al., 2015). Most notably is the extensive exploration performed in Park et al. (2020), which found that the Korean variant of the BDI not only displayed a significant correlation between the total score and subfactors of the assessment, but also that all 21 individual inventory items showed high levels of internal reliability and consistency. This reliability is reaffirmed in Viinamaki et al. (2004), which found that when a cut-off BDI score of 14/15 was used, almost all patients suspected by the clinician of having MDD, do in fact have it. One critical detail that should be of note, however, is that while BDI does in fact provide some insight into the potential

of a patient having MDD, it is also possible to receive a high BDI score without qualifying for an MDD diagnosis.

Because of the aforementioned commonality of MDD in MS, it is then beneficial to observe whether both the formation of lesions and structural brain abnormalities contribute to comorbid MDD. This complicates things further. A small scale study by Honer et al. (1987) revealed an association between increased temporal lobe lesion score and depression in MS patients. This however, was tested by Ron and Logsdail (1989), Feinstein et al. (1992), and Millefiorini et al. (1992), all of which were unable to replicate the 1987 study (Feinstein et al. 2004). Further, while Pujol et al. (1997) found an increased number of T2 lesions in the left arcuate fasciculus in MS patients, this only accounted for 17% of the variance in depression score.

Taken from a more recent study, there appears to be an association between the functional connectivity of the right amygdala, white matter volume, and fractional anisotropy of the left uncinate fasciculus with a total explained variance of 48% (Van Geest et al., 2019). Additional studies have found evidence linking frontal white matter atrophy to MS patients with MDD as seen in Feinstein et al. (2009) and Shen et al. (2014), as well as reduced limbic and frontal functional connectivity (Treadway & Pizzagalli, 2014; & Mulders et al., 2015). This notion of reduced fronto-limbic functional connectivity being linked to MDD is reaffirmed in Scheuer et al. (2017). It may then be possible to assume that the reduced white matter volume, as well as the scarred tissue present with the development of MS, may have contributed to this reduced functional connectivity, and therefore result in comorbid MDD.

2.5 The Importance of MRI in MS Research and Patient Follow-ups

The use of MRI in the diagnosis and research of MS is critical. As mentioned previously in Dobson and Giovannoni, (2018), it is a valuable tool to confirm a diagnosis of MS. Further, the utilization of T1 imaging allows for a greater visual contrast between myelin and cortex, resulting in a clear visualization of lesions (Hemond & Bakshi, 2018). This serves two purposes: First, the clearer imaging allows a more absolute diagnosis or dismissal of an MS diagnosis, beneficial for further action to be taken by the patient or neurologist, and second, in the case a diagnosis of MS was given, it allows for a constant assessment between patient follow-ups to

assess the effectiveness of drug intervention, as well as disease progression. In the latter, ææassessing disease progression with the accuracy awarded from T1 imaging, it would allow for a continuation, adjustment, or termination of a treatment method. This is the case for spinal cord lesions as well. The utilization of MRI allows for a more detailed observation of the spinal cord to detect white matter lesions as well as deterioration over time (Hemond & Bakshi, 2018).

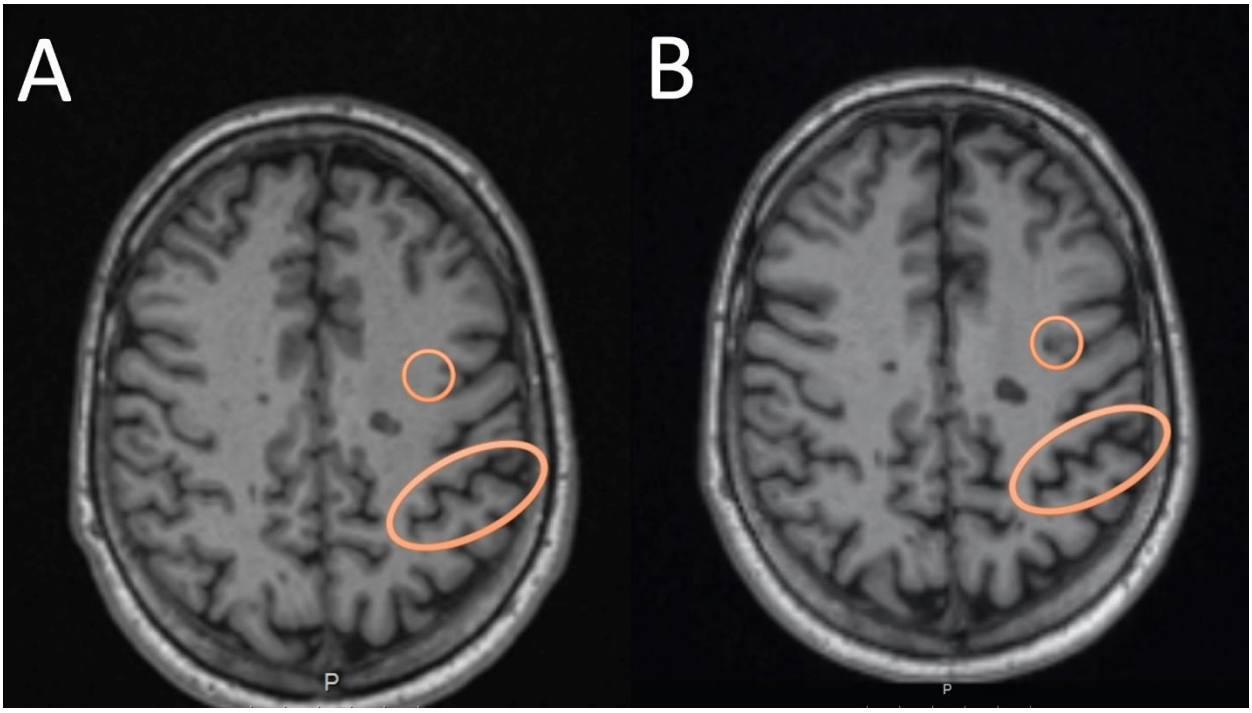

Fig 1. **Example of lesion progression in MS.** Reprinted with permission from Brune et al., in print.

2.6 Aims of this thesis

The primary goal of this thesis, was to investigate the association between comorbid depressive symptoms and lesion load in MS patients over an extended period of time. Further, we wanted to assess whether there was an association between increased depressive symptoms in relation to larger temporal lobe lesion volume. As the current body of literature lacks a thorough, longitudinal observation between comorbid depressive symptoms and temporal lobe lesion volume, this study seeks to contribute to the bridging of this gap.

We hypothesized that:

1. Average whole brain and right and left temporal lobe volumes will decrease between time points 1 and 3.

2. Higher BDI sum scores will correlate to temporal lobe lesion volumes at time point 1 and with higher rates of brain atrophy over time. An increase in BDI sum score would also be associated with an accelerated brain atrophy over time, indicating that as MS progresses, depressive symptoms becomes more prevalent.

3. Individual BDI item scores will increase from time point 1 until time point 4.

3. Materials and methods

3.1 Participants

Seventy-six MS patients at Oslo University Hospital were recruited for this study (Nygaard et al., 2015a; Nygaard et al., 2015b). All patients received a diagnose of MS, according to the revised McDonald Criteria (Polman et al., 2011), between January 2009 and December 2012, and were enrolled in the study approximately 14 months (±11.8) after the date of diagnosis (time point 1). Of the 76 patients, 75 received a primary diagnosis of RRMS, and one received a diagnosis of SPMS. Exclusion criteria included age < 18 years or > 50 years, ambiguous diagnosis, non-fluency in Norwegian, presence of other neurological or psychiatric diseases, drug abuse, head trauma, pregnancy and previous adverse reactions to gadolinium. Most patients also participated in three follow-up examinations on average 26 months (±11.7, time point 2, n = 60), 66 months (±13.3, time point 3, n = 62), and 78 months (±14.9, time point 4, n = 57) after the date of diagnosis. During each visit, and within the same week as their MRI scan, all patients completed a neurological examination by a Neurostatus certified medical doctor (http://www.neurostatus.com).

This study was carried out in accordance with the recommendations of the Regional Committee for Medical and Health Research Ethics with written and informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the South East Regional Committee for Medical and Health Research Ethics.

3.2 MRI acquisition

For consistency, the same 1.5 T scanner (Avanto, Siemens Medical Solutions; Erlangen, Germany) was used to acquire images from all MS patients for the first three time points, and a 3 T scanner at time point four between January 2012 and March 2019 in a combined research and clinical setting. A 12-channel head coil was utilized with the scanner. A 3D T1-weighted MPRAGE (Magnetization Prepared Rapid Gradient Echo) sequence was utilized in the collection of structural MRI data. The following parameters were used: TR (repetition time) / TE

(echo time) / flip angle / voxel size / FOV (field of view) / slices / scan time / matrix / time to inversion = 2400 ms / 3.61 ms / 8° / 1.20 x 1.25 x 1.25 mm / 240 / 160 sagittal slices / 7:42 minutes / 192 × 192 / 1000 ms. This MRI sequence was maintained during the scanning period. Additional FLAIR (Fluid attenuation inversion recovery), T2 and pre- and post-gadolinium 3D T1 sequences were attained and used for neuroradiological evaluation (Nygaard et al., 2015b).

3.3 MRI pre- and postprocessing

Using the T1-weighted scans we performed cortical reconstruction and volumetric segmentation with FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu/) (Dale et al., 1999). To extract reliable volume and thickness estimates, images included in the longitudinal 1.5T MRI dataset were processed with the longitudinal stream in FreeSurfer (Reuter et al., 2012). Specifically an unbiased within-subject template space and image was created using robust, inverse consistent registration (Reuter et al., 2010). Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations were then initialized with common information from the within-subject template, increasing reliability and power (Reuter et al., 2012).

Manual quality control of the MRI scans from patients was performed by trained research personnel to identify and edit segmentation errors where possible (n = 43 MRIs) and exclude data of insufficient quality (n = 6 MRIs). In addition, eight brain scans were removed due to missing sequences from MS patients. Lesion filling was performed utilizing automatically generated lesion masks from Cascade (Damangir et al., 2012) with the lesion filling tool (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/lesion_filling) in FSL (Jenkinson et al., 2012). The lesion masks were assessed by a trained neuroradiologist and normalized to MNI space using FLIRT (Jenkinson et al., 2002), with the corresponding T1 image as an intermediate. The lesion volumes for the temporal lobe used in this thesis are derived from the lesion masks at time point 1, using the automated Cascade pipeline.

3.4 Self-report questionnaires and clinical examination

In order to measure depression scores across all four time points, the Beck Depression Inventory-Second Edition was used (Beck, Steer, & Brown, 1996). This 21-item assessment allowed for an

easy, brief report from patients that would provide an assessment for the severity of their depression at that point in time. These included items that assess agitation, depleted energy, difficulty concentrating, and feelings of worthlessness. These items are assessed on a 4-point Likert scale with a score ranging from 0-3, indicating, within the past two weeks, the extent at which they experienced a certain item.

The Expanded Disability Status Scale (EDSS) is an assessment that allows for an observation of the severity of disability in MS patients at the time of administration. This assessment provides a score from 0 to 10 with increments of 0.5. MS patients with a score between 1.0 and 4.5, based on: pyramidal, cerebellar, brainstem, visual, and cerebral functionality, sensory systems, and bowel and bladder function. Individuals that fall within this score range are able to walk without any kind of assistance. Further, individuals who receive a score of 5.0 to 9.5 have difficulty walking without some form of assistance. To give an idea of each of the four scores discussed, a 1.0 would be indicated by the patient having no disability and minimal signs of MS in one functional system, a 4.5 is indicated by the patient having significant disability, but still able to walk without pause or assistance for 300m and perform a full day of work. A score of 5.0 would be indicated by a level of disability that impairs the individual's ability to work a full day without some form of support or assistance. A score of 9.5 would be complete confinement to a bed and dependence on others, with the inability to effectively communicate or to swallow. Lastly, a score of 10 is assigned when an individual dies due to MS (Kurtzke, 1983).

3.5 Statistical analyses

R (R Core Team, Vienna, 2018) was utilized for statistical analyses. All LME models accounted for age, age^2, sex and scanner (Bernal-Rusiel et al., 2013). A principle component analysis (PCA) was performed using the PCA function in the "FactoMineR" package (https://cran.r-project.org/web/packages/FactoMineR/index.html). Data was assessed for normality and outliers using the qqnorm and qqplot functions in the "stats v3.6.2" package. A linear mixed effect model was used to assess longitudinal data, and was performed using the lme function in the "nlme" package (https://CRAN.R-project.org/package=nlme). Figures were produced using the plot_model function in the "sjPlot" package (https://cran.r-project.org/web/packages/sjPlot/index.html), the ggplot function in "ggplot" package

(https://cran.r-project.org/web/packages/ggplot2/index.html), and the built-in plot function in RStudio.

4. Results

4.1 Descriptive Statistics of Participant Characteristics

The sample was initially comprised of 76 participants with the youngest participant aged 21 and the oldest aged 46 with an average age of 34.8 years. Of the 76 participants, 69.7% were female (n = 53) and 30.3% were male (n = 23). Further, participants had an average education of 14.9 years, with the lowest being 9 and the highest being 21. In terms of EDSS, participants had a median EDSS score of 2.0 and a range of (0 – 6) at time point 1. Additionally, participants had an average BDI sum score of 9.0 at time point 1. Table 1 provides a more comprehensive summary across the four time points.

Table 1. **Demographic and clinical characteristics for the MS sample at all time points.**

Characteristics	Time Point 1	Time Point 2	Time Point 3	Time Point 4
Number of Participants Total, n	76	56	61	50
Sex				
Female, n (%)	53 (69.7)	40 (71.4)	43 (70.5)	35 (70)
Male, n (%)	23 (30.3)	16 (28.6)	18 (29.5)	15 (30)
Age, mean, (range), [SD]	34.8, (21 – 49), [7.27]	38.1, (22 – 50), [7.34]	40.7, (25 – 53), [7.25]	41.6, (27 – 54), [7.05]
Education				
Years, mean	14.9	n.a.	n.a	n.a
BDI Score				
BDI sum, mean (SD)	9.0 (6.6)	8.3 (6.2)	7.6 (5.9)	8.0 (6.4)

EDSS Score				
EDSS, median (range)	2.0 (0 – 6)	2.0 (0 – 4)	2.0 (0 – 6)	n.a

4.2 Average Lesion and Brain Volumes

In order to observe the change in both brain and lesion volume, the mean volume (mm^3) was calculated at each time point. This is represented visually in figures 2a – 2f for brain volume, and numerically in table 2 for both brain and lesion volumes.

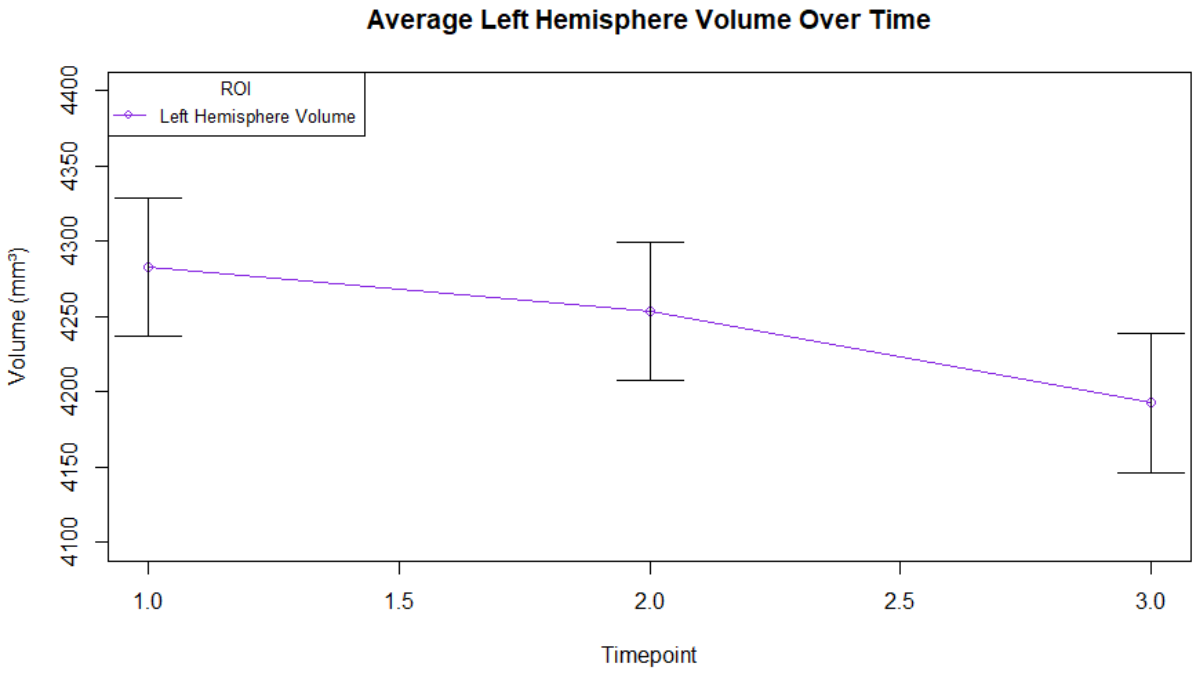

Fig 2a. **Average left hemisphere volume across all three time points.**

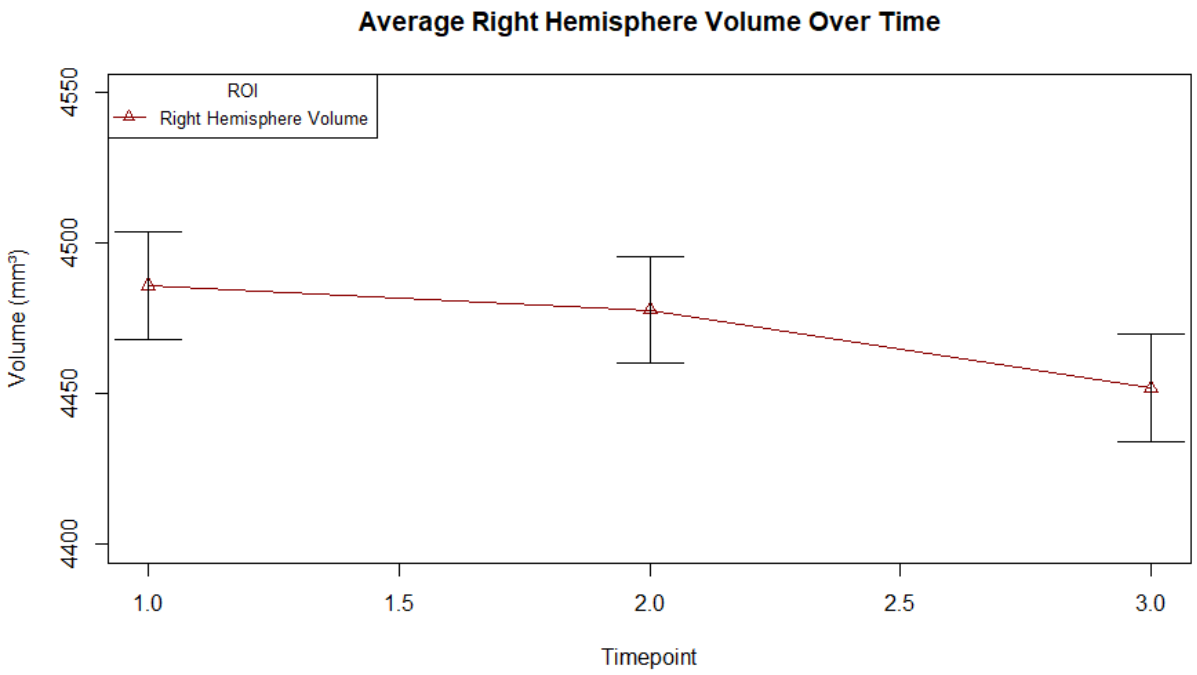

Fig 2b. **Average right hemisphere volume across all three time points.**

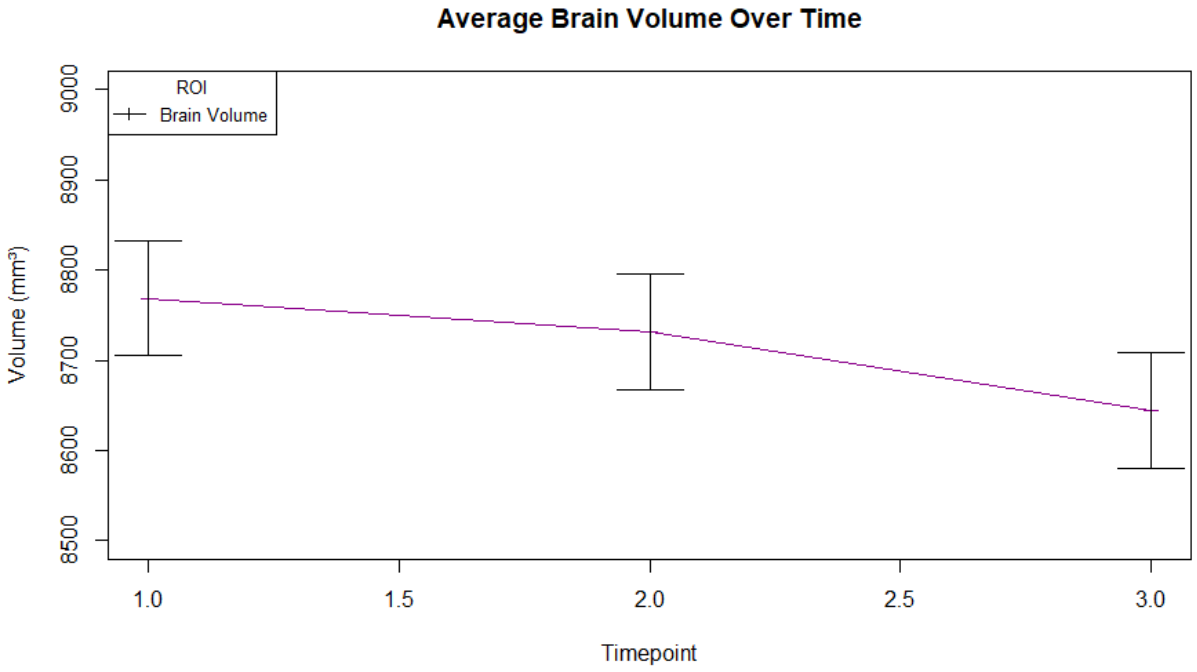

Fig 2c. **Average whole brain volume across all three time points.**

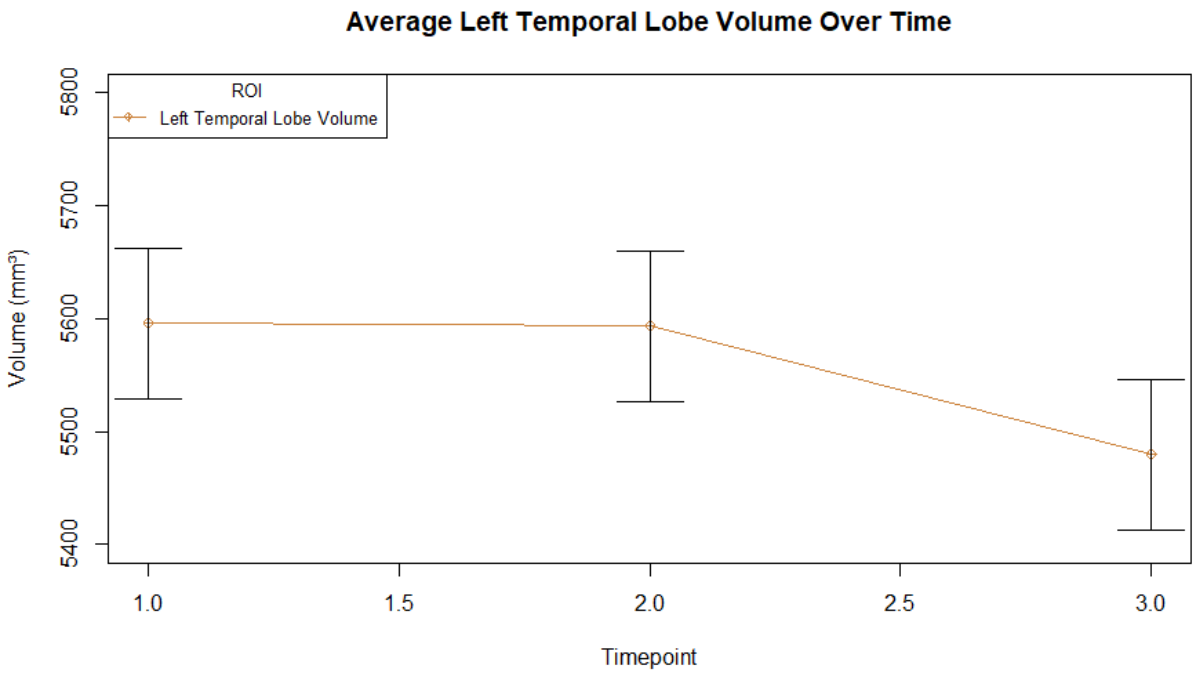

Fig 2d. **Average left temporal lobe volume across all three time points.**

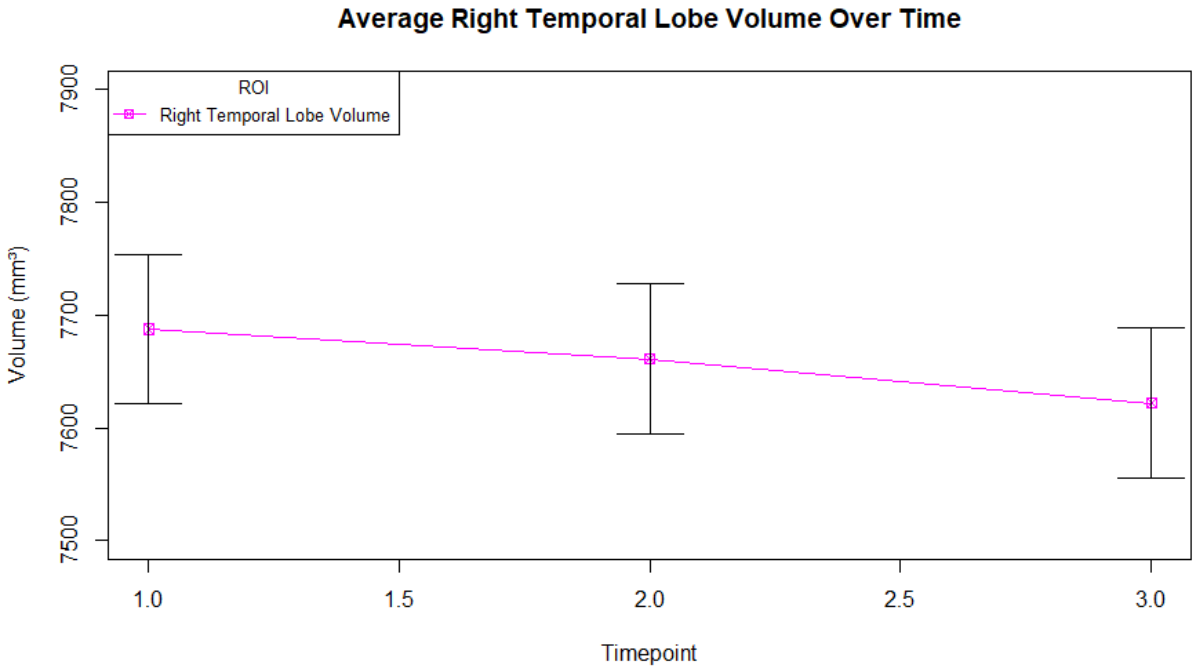

Fig 2e. **Average right temporal lobe volume across all three time points.**

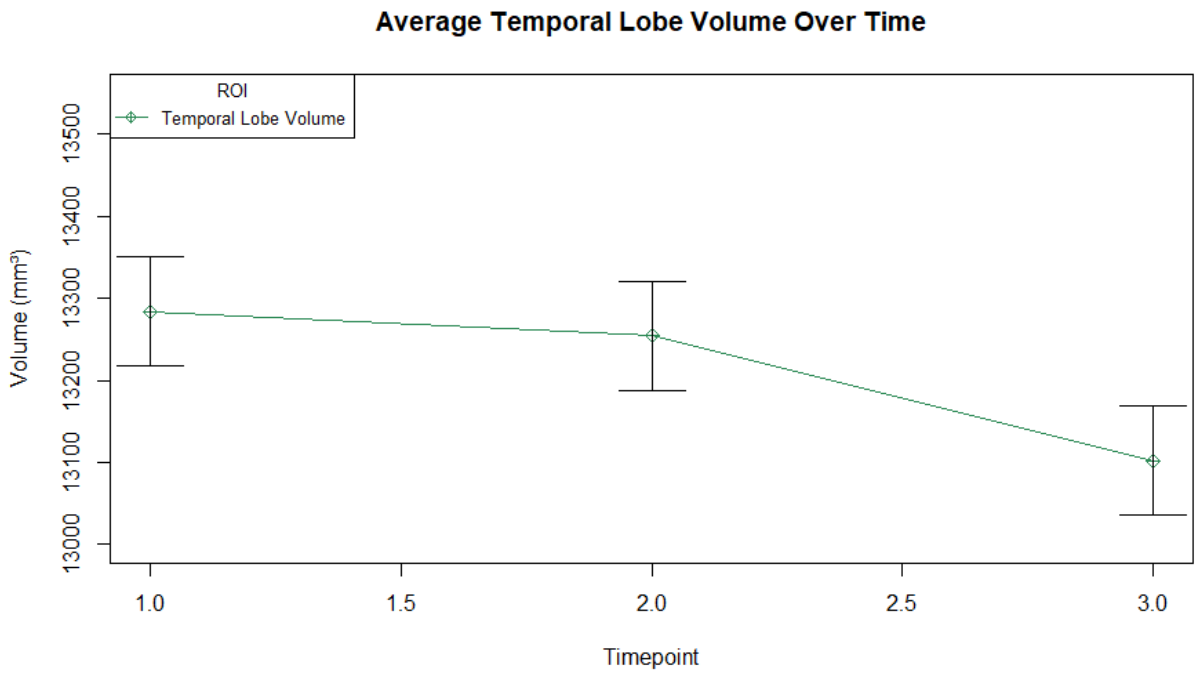

Fig 2f. **Average whole temporal lobe volume across all three time points.**

Table 2. **Average Brain and Lesion Volumes Over Time.** Green denotes an increase in volume from the previous time point, while red denotes a decrease in volume from the previous time point.

MRI Results	Time Point 1	Time Point 2	Time Point 3
Brain Volume			
Left Hemisphere, mean mm³, (SD)	4,282.932, (792.702)	4253.638, (883.246)	4192.7, (786.022)
Right Hemisphere, mean mm³, (SD)	4,486, (559.260)	4,477.931, (596.412)	4,451.833, (581.746)
Whole Brain, mean mm³, (SD)	8,768.932, (1,213.521)	8,731.569, (1,343.163)	8,644.533, (1,202.536)
Left Temporal Lobe, mean mm³, (SD)	5,595.849, (772.603)	5,593.5, (762.126)	5,479.667, (774.203)

Right Temporal Lobe, mean mm^3 (SD)	7,687.671, (938.349)	7,661.034, (1,036.771)	7,622.067, (986.758)
Whole Temporal Lobe, mean mm^3, (SD)	13,283.520, (1,537.752)	13,254.53, (1,662.166)	13,101.73, (1,580.067)
Lesion Volume			
Whole Brain, mean mm^3, (SD)	8,234.625, (4,822.958)	n.a	n.a
Right Temporal Lobe, mean mm^3, (SD)	834.780, (671.609)	n.a	n.a
Left Temporal Lobe, mean mm^3, (SD)	369.374, (394.261)	n.a	n.a

In order to check for a significant change between time points, a linear mixed effect model was used for each entry. Results showed that, when controlling for sex and age, there was no significant change in brain volume for any ROI between time point 1 and time point 3.

4.3 Longitudinal Analysis of BDI and Lesion and Brain Volume

In order to test the main hypothesis, a linear mixed effect model was utilized to compare the BDI sum score to the left, right, and total temporal lesion volume, as well as the total brain volume. Sex, Time Point, and the regions of interest were included as covariates in their respective assessments. These results can be seen in figures 3a – 3d.

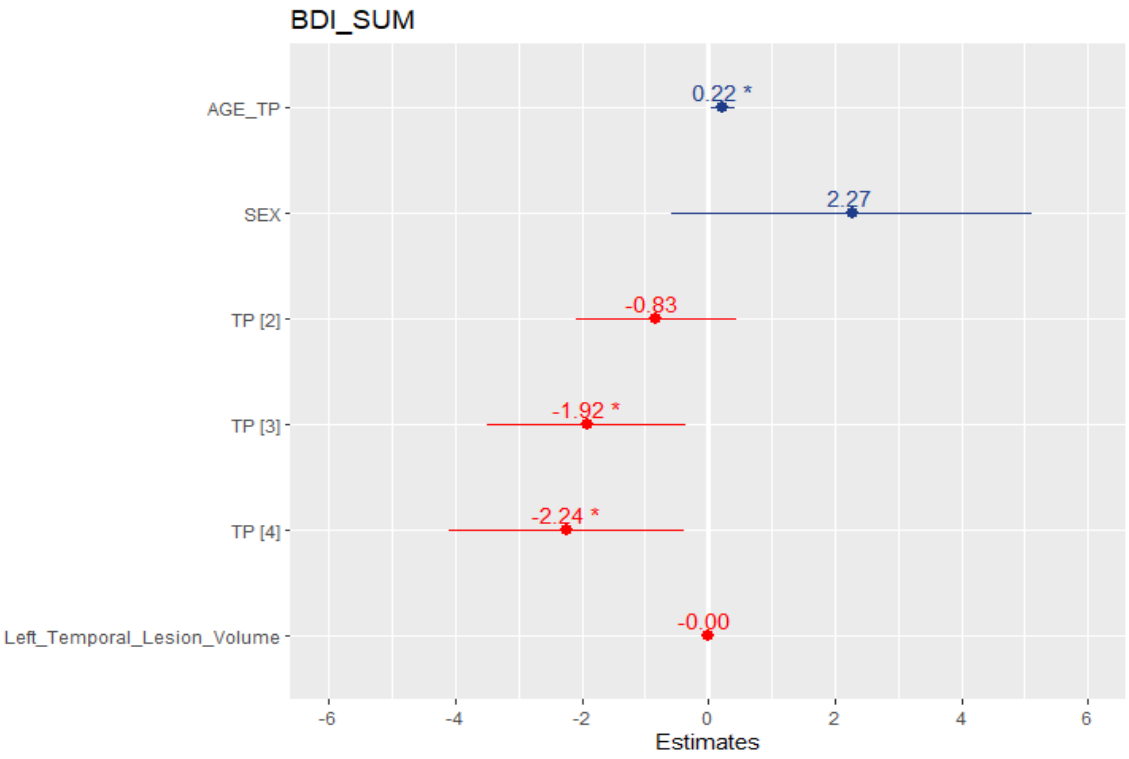

Fig 3a. **LME model of BDI sum and left temporal lesion volume.**
*denotes significance ($p < 0.01$)

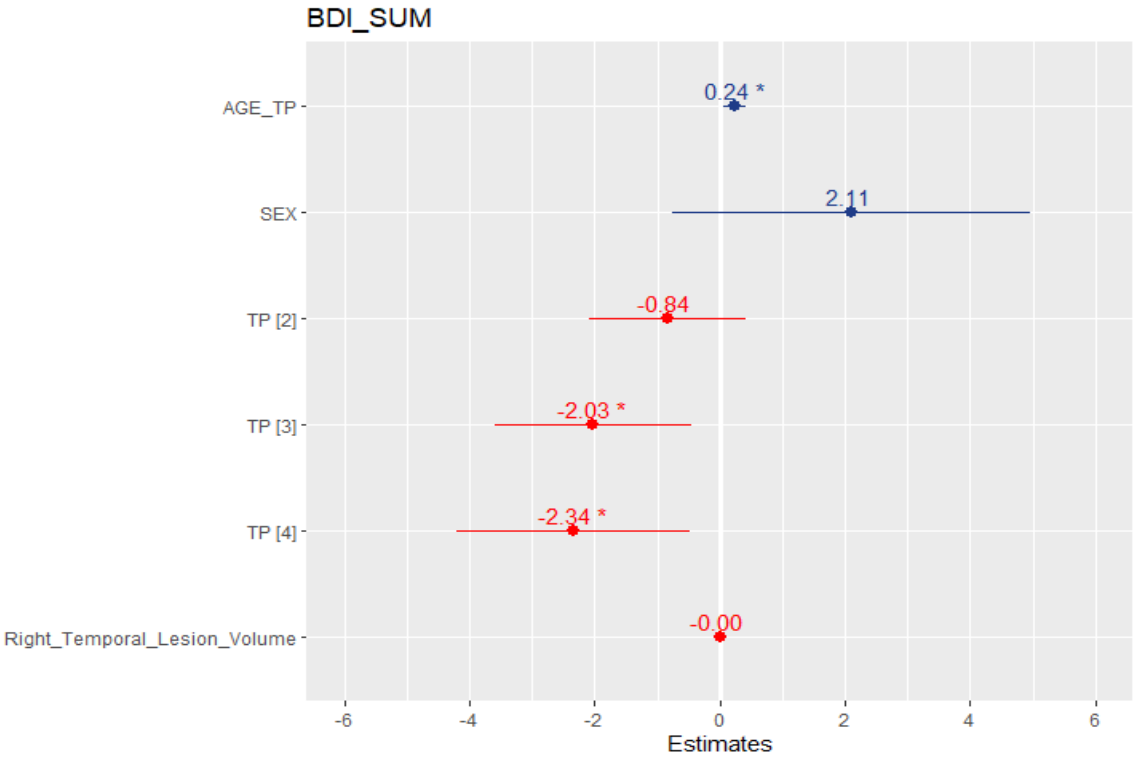

Fig 3b. **LME model of BDI sum and right temporal lesion volume.**
*denotes significance ($p < 0.01$)

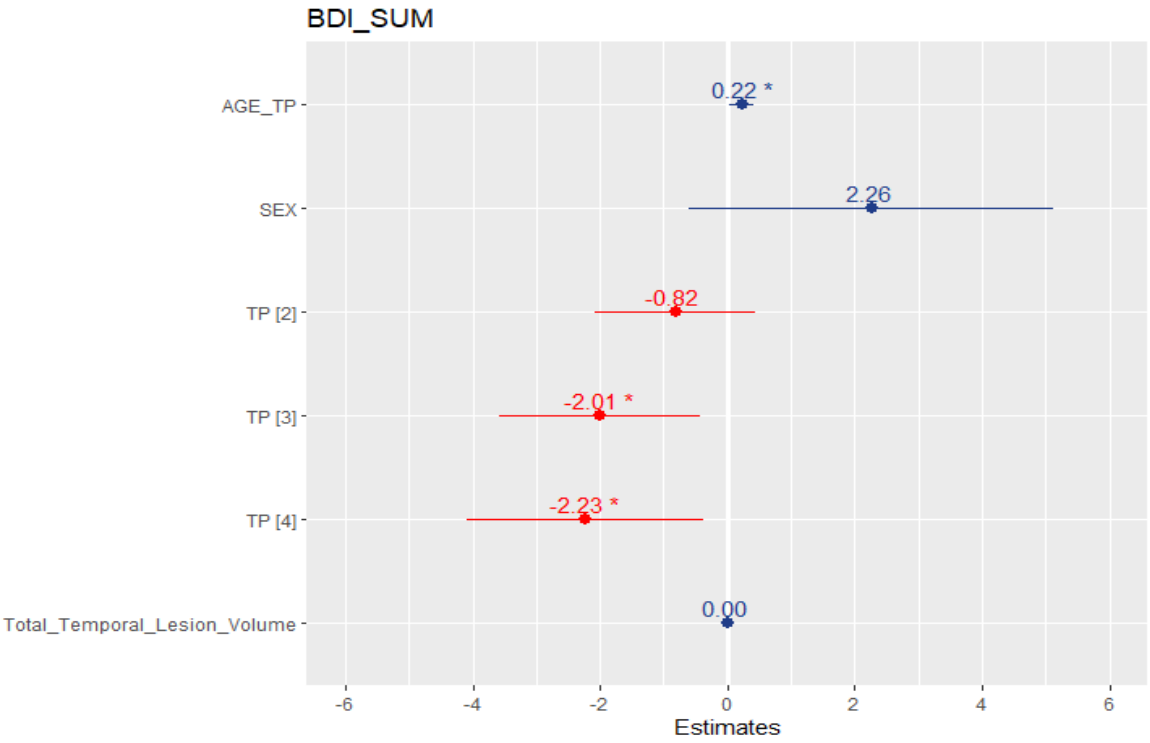

Fig 3c. **LME model of BDI sum and total temporal lesion volume.** *denotes significance ($p < 0.01$)

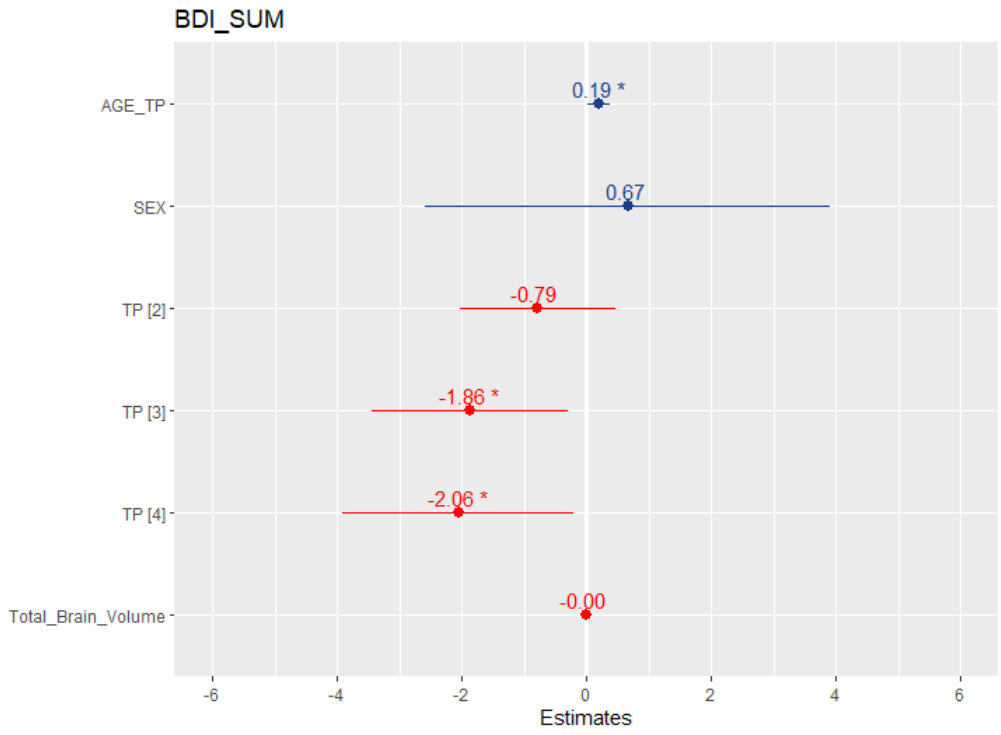

Fig 3d. **LME model of BDI sum and total brain volume.** *denotes significance ($p < 0.01$)

In observing the correlations between BDI sum and **left temporal lesion volume** (**Figure 3a)**, there was a significant positive correlation with the age of the participant at each time point (**AGE_TP)** ($t = 2.39$, $p = 0.01$). Further, there was a significant negative correlation between BDI sum and time point 3 ($t = -2.43$, $p = 0.01$) and time point 4 ($t = -2.37$, $p = 0.01$). Critical to the main hypothesis, there was no correlation between BDI sum score and left temporal lesion volume.

Oddly, an identical pattern exists between BDI sum score and each region of interest. In the observation of BDI sum score and **right temporal lesion volume (Figure 3b) AGE_TP** was positively correlated ($t = 2.54$, $p = 0.01$), and time points 3 and 4 were negatively correlated ($t = -2.55$, $p = 0.01$ and $t = -2.48$, $p = 0.01$, respectively). BDI sum score and **total temporal lesion volume (Figure 3c)** revealed a positive correlation with **AGE_TP** ($t = 2.40$, $p = 0.01$) and a negative correlation with time points 3 and 4 ($t = -2.52$, $p = 0.01$, & $t = -2.37$, $p = 0.01$, respectively). Lastly, the assessment of BDI sum score and **total brain volume (Figure 3d)** displayed a positive correlation with **AGE_TP** ($t = 2.08$, $p = 0.03$), and a negative correlation with time points 3 and 4 ($t = -2.34$, $p = 0.02$, & $t = -2.19$, $p = 0.03$, respectively). In this observation, the correlation between BDI sum score and total brain volume was approaching but did not meet significance ($t = -1.93$, $p = 0.057$).

4.4 BDI Question Score Averages

To further understand the change in BDI across all four time points, the mean score for each individual question, as well as the individual BDI sum scores were analyzed. Averaged individual scores are represented visually in figures 4a - 4c, and numerically in table 3. Individual BDI sum scores are represented visually in Figure 5.

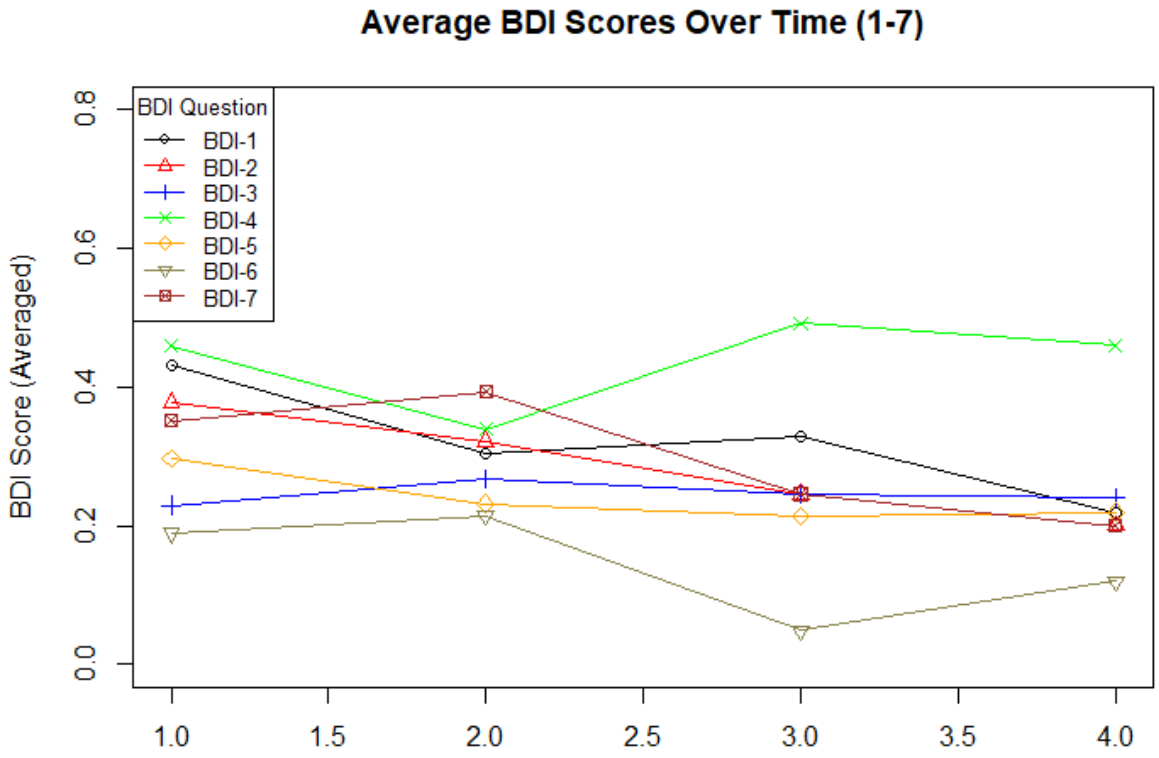

Fig 4a. **Averaged BDI scores for questions 1-7 across all four time points.**

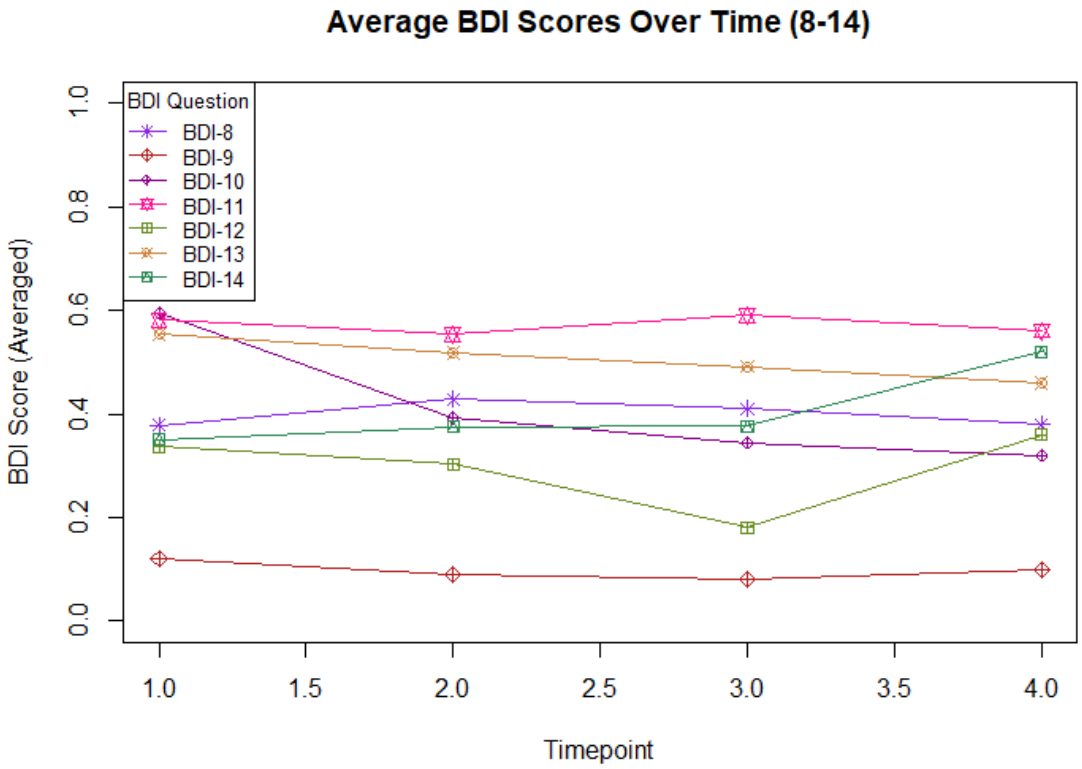

Fig 4b. **Averaged BDI scores for questions 8-14 across all four time points.**

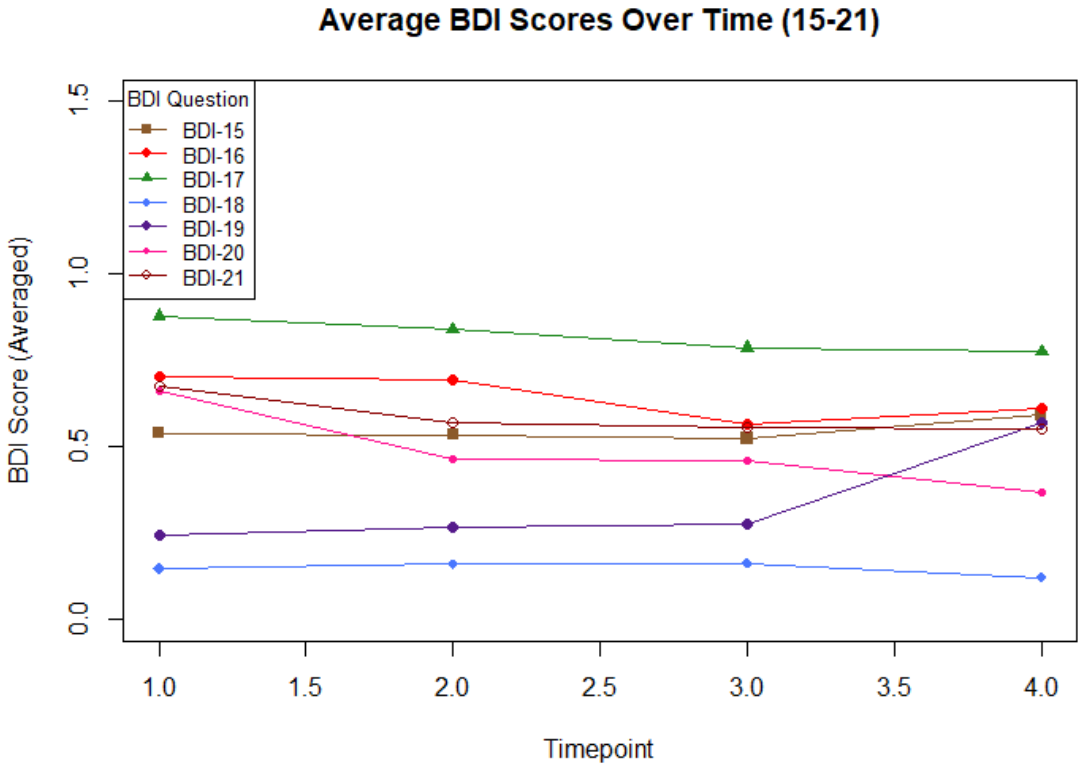

Fig 4c. **Averaged BDI scores for questions 15-21 across all four time points.**

Table 3. **Average BDI Scores at all four Time Points** Green denotes a lower average depression inventory score, red denotes a higher average depression inventory score, and yellow denotes no change. These changes are observed between Time Point 1 and 2, 2 and 3, & 3 and 4. * denotes $p < 0.05$ | ** denotes $p = 0.01$ | *** denotes $p < 0.01$

BDI Question	Time point 1	Time Point 2	Time Point 3	Time Point 4
BDI-1, mean (SD)	0.43 (0.58)	0.30 (0.46)	0.33 (0.51)	0.22 (0.42)**
BDI-2, mean (SD)	0.38 (0.59)	0.32 (0.61)	0.25 (0.54)	0.20 (0.45)***
BDI-3, mean (SD)	0.23 (0.48)	0.27 (0.49)	0.25 (0.43)	0.24 (0.48)
BDI-4, mean (SD)	0.46 (0.55)	0.34 (0.51)	0.49 (0.57)	0.46 (0.50)
BDI-5, mean (SD)	0.30 (0.49)	0.23 (0.50)	0.21 (0.52)	0.22 (0.46)
BDI-6, mean (SD)	0.19 (0.57)	0.21 (0.71)	0.05 (0.22)	0.12 (0.48)
BDI-7, mean (SD)	0.35 (0.58)	0.39 (0.53)	0.25 (0.43)	0.20 (0.40)**
BDI-8, mean (SD)	0.38 (0.54)	0.43 (0.60)	0.41 (0.59)	0.38 (0.57)
BDI-9, mean (SD)	0.12 (0.33)	0.09 (0.29)	0.08 90.28)	0.10 (0.30)
BDI-10, mean (SD)	0.59 (0.76)	0.39 (0.59)	0.34 (0.57)	0.32 (0.68)*
BDI-11, mean (SD)	0.58 (0.57)	0.55 (0.51)	0.59 (0.53)	0.56 (0.61)
BDI-12, mean (SD)	0.34 (0.53)	0.30 (0.50)	0.18 (0.43)	0.36 (0.53)
BDI-13, mean (SD)	0.55 (0.76)	0.52 (0.74)	0.49 (0.74)	0.46 (0.71)
BDI-14, mean (SD)	0.35 (0.69)	0.38 (0.59)	0.38 (0.71)	0.52 (0.86)
BDI-15, mean (SD)	0.54 (0.71)	0.54 (0.69)	0.52 (0.59)	0.59 (0.64)
BDI-16, mean (SD)	0.70 (0.84)	0.70 (0.85)	0.57 (0.74)	0.61 (0.72)*
BDI-17, mean (SD)	0.88 (0.57)	0.84 (0.65)	0.79 (0.64)	0.78 (0.65)**
BDI-18, mean (SD)	0.15 (0.36)	0.16 (0.42)	0.16 (0.37)	0.12 (0.33)
BDI-19, mean (SD)	0.24 (0.68)	0.27 (0.73)	0.28 (0.70)	0.57 (1.05)
BDI-20, mean (SD)	0.66 (0.63)	0.46 (0.54)	0.46 (0.53)	0.37 (0.52)***
BDI-21, mean (SD)	0.68 (0.80)	0.57 (0.83)	0.56 (0.62)	0.55 (0.64)

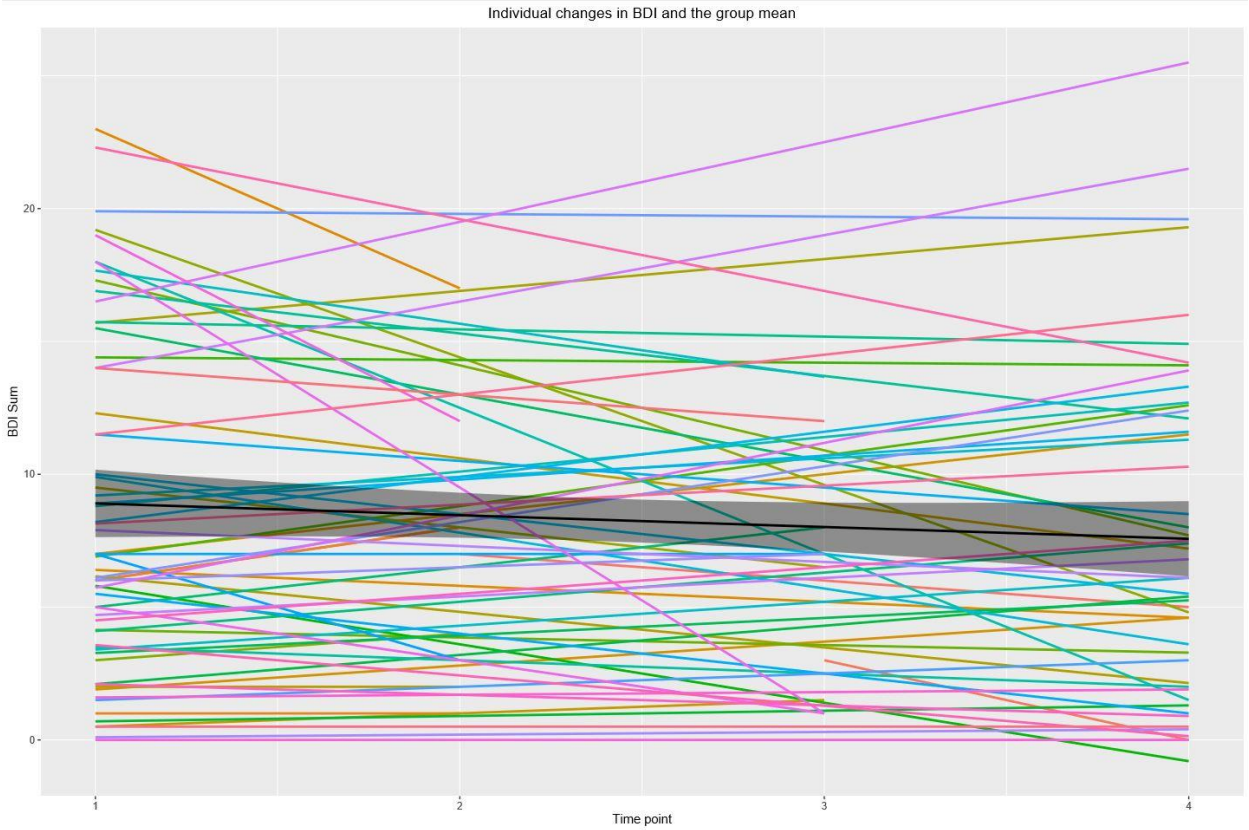

Fig 5. **BDI sum scores across all four time points.**

Most notable when observing the average BDI sum scores in **Table 1,** the decline in the average scores for each individual BDI question in **Figure 4a – 4c** and **Table 3**, and the decline in individual BDI sum scores in **Figure 5**, is that they remain in the lowest score subset of the Beck Depression Inventory, with an indication that the presence and subsequent absence of depressive symptoms experienced is within the normal range.

In terms of the individual BDI item scores, a linear mixed effect model revealed that, when controlling for both sex and age, 7 of the 21 BDI questions showed a significant decrease in score between Time Point 1 and Time Point 4: BDI-1 ($t = -2.6$, $p = 0.01$), BDI-2 ($t = -2.7$, $p = 0.007$), BDI-7 ($t = -2.4$, $p = 0.01$), BDI-10 ($t = -2.2$, $p = 0.02$), BDI-16 ($t = -2.1$, $p = 0.03$), BDI-17 ($t = -2.5$, $p = 0.01$), & BDI-20 ($t = -3.7$, $p = 0.00$), and that 1 of the 21 BDI questions showed a significant increase in score between Time Point 1 and Time Point 4: BDI-19 ($t = 3.1$, $p = 0.00$). Those that showed a significant decrease corresponded to feelings of sadness, pessimism, self-dislike, frequency of crying, changes in sleeping patterns, irritability, and tiredness and

fatigue respectively, while BDI-19 corresponded to a significant increase in concentration difficulty.

5. Discussion

5.1 Primary Results

In the present study, ROI-specific lesion volumes, mean brain volume, the association between summed BDI scores and specified regions of interest, and the longitudinal change in mean BDI question scores were examined.

The longitudinal change in full brain volume is an important element to examine in MS, with the current study finding a reduction in brain volume at time point 3 compared to time point 1. Notably, Cheriyan et al. (2012) found a similar trend, with an overall reduction in brain volume over a one year period, and active lesions being an independent predictor of said loss in volume. This overall reduction is further supported by Kalkers et al. (2002), which reported a longitudinal decrease in brain volume regardless of MS phenotype.

The results of the current study reflect those found in Cheriyan et al. (2012) and Kalkers et al. (2002), with a decrease in average whole brain, and temporal lobe lesion volume from time point 1 to time point 3, thus confirming hypothesis 1. While these results are unsurprising, it is critical to further understand what may be influencing this decline in volume. Notable are the results found in Radue et al. (2015), which found that in a total of 3,653 MS patients, disability, both T1 and T2 lesion volume, aging, and disease duration were all significantly associated with a decrease in brain volume. This may then be the case with the present results, with aging being a significant contributor to a longitudinal study. As lesion volume was only available for time point one, it is not possible to say whether this played a role in the current outcome of this study. However, as lesions are a core component of MS, further understanding the effect they have on MS patients in both an immediate and longitudinal framework is of immense importance.

The assessment of BDI in relation to lesions in MS presents results similar to those hypothesized (Berg et al., 2000; Mohr et al., 2003; Pujol et al., 2000; & Berg et al., 2000). Noted in Berg et al. (2000), was the significantly higher lesion load in the temporal lobes in depressed MS patients

with a significant correlation to BDI score. More specifically, it appeared that the right temporal lobe was more prominent compared to the left temporal lobe in this correlation. Similar to Berg et al. (2000) is Mohr et al. (2003), which reported that the post-treatment BDI score was significantly predicted by greater lesion volume in both the left temporal lobe and right periventricular temporal horn. Lastly, Pujol et al. (2000) presents a similar result, in that lesions in the left arcuate fasciculus accounted for 26% of BDI symptoms and that this correlation was statistically significant. Taken together, the results of these studies suggest some association between lesion load in the temporal lobe, or lesions in regions associated with the temporal lobe, and BDI score.

In comparison to the aforementioned association between BDI and lesion load, hypothesis 2, as found in the present study, failed to reproduce similar results, finding no significance between temporal lobe lesion volume, or total brain volume and BDI sum score. However, based on the literature search for this thesis, it seems more likely that either an inappropriate method was used in assessing the current data, or that, as mentioned before, the continual changing of participant numbers negatively impacted the overall results of the study.

Concerning hypothesis 3, the original belief was too extreme and assumed, incorrectly, that depressive symptoms, regardless of category, would follow a steady trend and increase over time. This was not the case, and instead fluctuations were seen from time point 1 to time point 4. It would be immensely beneficial, then, to further explore MS using the various symptoms of depression, rather than depression as a single entity.

While seemingly counterintuitive, the trend for depressive symptoms to decrease over time in MS has been reported on countless times. Brown et al. (2009), for example, observed that during a 24 month period, patients had both lower depression (assessed using BDI-II) at 24 months compared to 0 months, with a comparative score range of 0 – 26 at month 0 and 0-22 at month 24. However, in regards to depression, it should be noted that a more careful observation should be taken. Beal et al. (2007) reported that while depressive symptomology fluctuated at the individual level in 607 MS participants over a seven year span, there was no overall significant change in depressive symptoms at the group level. In reaffirmation to the fluctuation of depressive symptoms, Arnett and Randolph (2006) reports that a significant component in the

contribution to depressive symptomology in MS is the use of effective coping mechanisms, with their absence leading to increased bouts of negative mood. In this, hypothesis 3 extends further. While there were seven individual BDI item scores that showed a significant change over time, there was no significant change in the overall BDI sum score from time point 1 to time point 4, similar to the lack of group change in Beal et al. (2007). Further, it may be possible that each individual item, even when significant, has a different level of association with depression, a notion supported in Park et al. (2020).

This then leads to the possibility that the significant decrease in depressive symptoms in the present study, most notably between time points 1 and 4, might stem from the gradual adjustment to MS despite its progression. It may then be considered that due to the extensive time participants have had to manage their symptoms and find ways to adjust their lives for greater convenience and daily functioning, that they have grown accustomed to the current limitations and capabilities they have. This new definition of normality may act as a coping mechanism leading to the reduction of the overall feeling of depression.

Prior to exploring the external factors that may have influenced the results of this study in section **5.2**, it may prove beneficial to observe the association between depression and EDSS scores. Mattioli et al. (2011) reported that EDSS scores acted as predicting factor of depression in MS patients, and Tsivgoulis et al. (2007) found a significant, independent association between EDSS and BDI scores. Interestingly, both EDSS and BDI scores remained consistently low from time point 1 to time point 3 and time point 1 to time point 4, respectively, in the current study. This may be a result of the wider variations of drugs and treatment methodologies available to MS patients. Gajofatto and Benedetti (2015) presents an assessment of varying treatment plans for MS, which change based on MS phenotype and disease progression. If true, it is possible that the lower BDI and EDSS scores may be attributed to patients in the current study receiving the appropriate treatment, as well as a changing their treatment plan as their symptoms change.

5.2 Potential Explanations of External Influences on Current Results

Certainly then, there is need for speculation on additional external factors outside of the clinical results, which may aid in explaining the current findings of this study. One notion of continual interest, is the location of the current study. Since all patients had access to Norway’s public

healthcare system, and received their diagnosis and treatment in Norway, it may be of great interest to look at a review of the Norwegian healthcare system. Notably, Ringard et al. (2013)'s review of Norway's healthcare system revealed that mental health services, especially for the younger population are covered as preventative services. Further, mental health care is integrated with the individual's GP, who is responsible for following up with the patient. In tandem with this, is the obligatory prescription of the cheapest available equivalent product or medication unless otherwise specified. Lastly, Norway's healthcare system uses a cost-sharing ceiling which caps the (at the time of publication) yearly maximum personal contribution by the patient at 1,980 NOK or approximately $198.

Due to the reduced and manageable costs of healthcare in Norway, as well as a strong focus on mental health issues and the lack of pushing expensive treatment methods as a primary service, it becomes more likely that individuals experiencing issues or atypical symptoms feel less financial burden going to their GP or the hospital in order to, in this case, receive testing for a potential MS diagnosis. This same mindset may then carry over into further checkups and assessments; visiting a doctor based around a change in symptoms or for a timed follow up, rather than as a financial decision. If true, then the use of appropriate medication follows suit, with access to affordable products, as well as a reimbursement system in place, the out of pocket strain is dramatically reduced, and a more thorough treatment of symptoms is, in theory, promoted.

The basis for this belief of behavior comes from Rice et al. (2013)'s review of the United States healthcare system, which reported that individuals without insurance may avoid mental health treatment due to the associated out of pocket costs. Further, according to Cunningham (2009), there was not only a shortage of mental health providers in the United States, but also a difficulty for GPs in providing outpatient mental health care for their patients. This is accompanied by a difficulty in getting non-emergency hospital services for mental health. Solway et al. (2010) reported that an approximate 25% – 33% of children and 50% of older adults were unable to receive necessary mental health care. Another issue is the reluctance to fill a prescription due to high medication costs. Sorensen et al, 2004 revealed that in many instances, patients unable to afford another prescription either segmented their medication in an attempt to make it last longer, or settled for cheaper, less effective drugs.

It is then highly plausible that the severity of MS becomes a combination of the disease itself as well as the societal challenges present. This is observable in Reilly et al. (2017), which reported that MS patients in North America, compared to Europe had a lower physical and mental quality of life, as well as a higher positive depression screen. Should the results of this study be viewed as stemming from a reduction in societal challenges typically faced by MS patients without access to a more comprehensive healthcare system, a novel model of treatment strategies could be developed and implemented to reduce the severity of physical and mental symptoms, and improve patient quality of life.

5.3 Limitations

There are a few limitations that need to be addressed. Firstly was the sample size of the current study. The initial 76 was a modest but fairly robust number of participants. However, the constant fluctuation of total participants both complicated the data analysis, and led to several individuals being removed from the analysis entirely. While results of the current study were similar to previous reports, the sudden decline in volume between time point 2 and time point 3 may reflect the population that returned at time point 3. If, at that time, a majority of patients presented with worse symptoms, this could account for the noticeable, sharp decline. Further, the availability of lesion volumes at time point 1 only did not allow for a proper analysis of their change over time, and as a result their impact may have been underestimated.

5.4 Future Studies

Going forward, it would be incredibly beneficial to include groups of MS patients in different countries with varying country conditions to fully assess to what extent the current healthcare structures contribute to the overall management and treatment of symptoms as disease progresses. Further, a larger sample size and greater range of regions of interest would provide a more accurate and comprehensive analysis of the role of individual brain regions in both BDI score and the subsequent, if any, development of comorbid depression in MS patients. Ideally, a 10 year study consisting of early-diagnosed MS patients from each continent with a monitoring of diet, drug and physical therapies, BDI and EDSS scores, and MRI scans, as well as an analysis of country conditions and financial burden, would provide an immensely comprehensive understanding of the progression of MS as well as an ideal treatment plan.

6. Conclusion

MS continues to be an immensely complex neurodegenerative disease that greatly impacts those that have it. However, it appears that with sufficient access to treatment, it is possible to reduce symptomology and progression over time, and greatly improve the quality of life of those afflicted with it. While the current study was unsuccessful in the confirming the association between BDI score and lesion volume, and increase in BDI score over time, it did find that average brain volume decreased over time, reconfirming previous reports. However, further research is required to more adequately understand the longitudinal changes in MS and their effects on those with this debilitating disease.

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