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CEREBRAL ACTIVATION DURING WORKING MEMORY IN MULTIPLE SCLEROSIS
WITH AND WITHOUT THE APOE EPSILON-4 ALLELE

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ABSTRACT

Introduction: Increased cerebral activation patterns have been demonstrated during working memory tasks using functional magnetic resonance imaging (fMRI) in individuals diagnosed with multiple sclerosis (MS) and in cognitively intact persons genetically at risk for Alzheimer's disease. Few studies have compared brain activation patterns associated with working memory as a function of apolipoprotein E (APOE) genotype in individuals with MS, despite evidence suggesting APOE's role in myelin formation, myelin repair, and neuronal plasticity processes. The purpose of this study was to determine whether the $\epsilon 4$ allele of the APOE gene influences brain activation in a sample of cognitively similar patients with MS.

Method: The sample ($N = 41$) was composed of 13 APOE- $\epsilon 4+$ and 28 APOE- $\epsilon 4-$ patients with MS. All participants completed a full neuropsychological assessment battery prior to undergoing fMRI to perform the N-back task used to probe working memory-related brain activity. Using Statistical Parametric Mapping 8 (SPM8), a two-sample t -test was used to compare brain activation in APOE genotype groups.

Results: Independent samples t -tests verified APOE group equivalences in demographic characteristics and on neuropsychological performance variables. The APOE- $\epsilon 4$ positive group exhibited greater activity in the medial frontal regions bilaterally and in the right dorsolateral prefrontal cortex, ($p < .001$, uncorrected with a minimum cluster size of 30 voxels).

Discussion: Given that APOE groups were equivalent demographically and cognitively, group differences in brain activation can be attributed to APOE genotype. The greater activation observed in APOE- $\epsilon 4$ carriers may suggest a compensatory mechanism to offset inefficient cognitive processes that occur when the brain is impacted by MS and the APOE- $\epsilon 4$ allele.

TABLE OF CONTENTS

LIST OF FIGURES	iii
LIST OF TABLES	iv
ACKNOWLEDGEMENTS	v
Introduction.....	1
Background	1
Functional Neuroanatomy of Multiple Sclerosis	1
APOE & Healthy Controls.....	3
APOE & Individuals with Multiple Sclerosis	4
Study Goals	5
Hypotheses	6
Methods.....	6
Participants.....	6
Neuropsychological Testing.....	7
Statistics	12
Magnetic Resonance Imaging	12
Genetics.....	16
Results	16
Participant Demographic Characteristics	16
Neuropsychological Variables in APOE- ϵ 4+ and ϵ 4- Patients with MS	17
Brain Activation Results	17
Discussion.....	19
Conclusion	24
References.....	25

LIST OF FIGURES

Figure 1: <i>N</i> -back Working Memory Task One- and Two-Back Conditions (derived Wishart et al., 2006)	13
Figure 2. Statistical Parametric Maps of Differential Contrasts in Brain Activation (APOE- ϵ 4 Positive > APOE- ϵ 4 Negative) during 2-back Condition ^a	19

LIST OF TABLES

Table 1 MS Sample Characteristics in APOE Allele Groups	17
Table 2 APOE Group Equivalences on Neuropsychological Performance	18
Table 3. Activated Brain Regions during Working Memory (2-back task) in MS Individuals with and without the APOE- ϵ 4 Allele.....	19

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Introduction

Background

Characterized as one of the most common neurodegenerative conditions diagnosed in young adulthood, multiple sclerosis (MS) affects nearly 1 million individuals in the United States and 2.3 million people worldwide (Rao, 1990; National Multiple Sclerosis Society, 2017). MS is a debilitating autoimmune disease resulting in highly variable cognitive, sensory, motor, and neuropsychiatric deficits (Arnett, Cadden, Roman, & Guty, in press; Brassington & Marsh, 1998). Symptom severity has been found to be related to the distribution and size of the brain atrophy and white matter plaques thought to interfere with the transmission of neural signals via the myelin sheath (Arnett & Strober, 2014; Chiaravalloti et al., 2005; Rumrill, Kaleta, & Battersby, 1996). While MS symptom presentation varies among individuals, cognitive impairment—particularly deficits in attention, concentration, executive functioning, processing speed, and working memory—is frequently observed in approximately 45% to 65% of persons with MS (Arnett & Strober, 2014; Hillary et al., 2003; Forn et al., 2007).

Functional Neuroanatomy of Multiple Sclerosis

Understanding the functional neuroanatomy of MS is important in identifying the mechanisms underlying and contributing to cognitive impairment (Arnett & Strober, 2014; Forn et al., 2007). In recent years, several functional magnetic resonance imaging (fMRI) studies

observed that patients with MS, compared to those without MS, exhibited an increase in brain activity when completing cognitively demanding tasks. For example, in a study comparing brain activation patterns of patients with MS to healthy controls during an auditory working memory task (i.e. the n-back), Forn et al. (2007) found that patients with MS displayed significantly greater activation in the prefrontal cortex bilaterally, specifically in Brodmann's area 44 (BA 44) and the insula. Of note, the two groups were comparable in terms of mean accuracy on the n-back task. Forn et al. (2007) attributed the intact n-back performance and increased brain activation to the adaptive recruitment of surrounding brain areas, positing it to be a compensatory mechanism. Sweet, Rao, Primeau, Mayer, & Cohen (2004) observed similar increased activation in the dorsolateral prefrontal cortex during working memory tasks in people with MS, further suggesting that increased activation is necessary to offset inefficient cognitive processing that occurs when the brain is impacted by MS.

During the modified Paced Auditory Serial Addition Test (mPASAT), Chiaravalloti et al. (2005) found that cognitively impaired MS patients, relative to cognitively intact MS patients and healthy controls, exhibited increased activation patterns in the right parietal and right frontal lobe regions. Similarly, Cader, Cifelli, Abu-Omar, Palace, & Matthews (2006) observed altered inter-hemispheric interactions in similar regions, particularly in the dorsal and lateral prefrontal regions, in individuals with MS who completed a verbal working memory task. While a number of studies suggest that adaptive properties of the brain drive increased cortical activation, Cader et al. (2006) proposed that this mechanism may actually preserve cognition, ultimately deferring the progression of the disease and cognitive deficits. In a review of prefrontal modulation of working memory performance in clinical populations, Hillary, Genova, Chiaravalloti, Rympha, & DeLuca (2006) observed similar right dorsolateral prefrontal activation patterns when cerebral

resources are challenged across multiple studies of varying clinical populations. Therefore, increased cortical activation in these regions may serve as a compensatory mechanism to maintain intact performance or modulate functioning on certain cognitively demanding neuropsychological tasks (Forn et al., 2007; Hillary et al., 2003; Hillary et al., 2006; Staffen et al., 2002).

APOE & Healthy Controls

The apparent compensatory process discovered in MS is not just observed in these patients. In fact, a study, conducted by Wishart et al. (2006), examining working memory in cognitively intact adults with varying allele genotypes of the apolipoprotein E (APOE) gene, exhibited differences in brain activation. Individuals' genotypes present as any homozygous or heterozygous pair of the following allelic variants: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ (Ghaffar, Reis, Pennell, O'Connor, & Feinstein, 2010). Each combination results in distinct protein isoforms that perform varying biological roles. The presence of one $\epsilon 4$ allele doubles the risk of Alzheimer's disease, while increase in risk is fivefold when two $\epsilon 4$ alleles are present (Mayeux (2003). In regards to the Wishart et al. (2006) study, relative to individuals without any APOE- $\epsilon 4$ alleles, cognitively intact participants with the heterozygous APOE- $\epsilon 4$ genotype demonstrated greater activation in the medial frontal and parietal regions bilaterally and in the right dorsolateral prefrontal cortex during an auditory verbal N-back task. Given that the APOE- $\epsilon 4$ allele is most commonly known as the susceptibility gene for developing Alzheimer's disease, this "upregulation of [brain] activity" may be indicative of alternative neural recruitment to compensate for the genetic risk of

cognitive impairment and maintain normal cognitive functioning (Ghaffar et al., 2010; Bookheimer et al., 2000; Wishart et al., 2006, p. 1606).

APOE & Individuals with Multiple Sclerosis

While the APOE gene is most commonly associated with Alzheimer's disease, studies have found evidence linking the APOE- ϵ 4 allele to less efficient myelin formation and repair as well as neuronal plasticity processes (Ghaffar et al., 2010). At the neuronal level, the protein produced by the APOE- ϵ 4 allele relative to the protein produced by the ϵ 3 allele is less effective in moderating lesion damage as observed in transgenic mice. After transgenic mice were inserted with human APOE- ϵ 3 or ϵ 4 alleles and experienced lesions of the entorhinal cortex, more pronounced post-lesion neurodegeneration was observed in ϵ 4 mice compared to ϵ 3 mice (White, Nicoll, Roses, & Horsburgh, 2001). Moreover, Teter et al. (2002) suggest that the lipoprotein produced by the APOE- ϵ 4 gene is indicative of suppressed regeneration, as evidenced by the decreased sprouting of granule cell mossy fibers following injury in hippocampal slice cultures of mice. In humans with MS, carrying the ϵ 4 allele is associated with significantly higher progression index of disability and higher MS severity score (Fazekas et al., 2001).

With evidence suggesting a relationship between the APOE- ϵ 4 gene and similar processes affected in MS, examining the role of APOE in an MS population is relevant (Ghaffar et al., 2010). Therefore, the influence of the APOE gene on common sequelae observed in MS populations has been studied more frequently in recent years (Burwick et al. 2006; Fazekas et al., 2001; Sylantiev, Chapman, & Chilkevich, 1998; Dousset, Gayou, Brochet, & Iron, 1998; Evangelous, Jackson, Beeson, & Palace, 1999; Hùgh et al., 2000). There is little research

examining the effect of APOE in MS on cognitive dysfunction; however, there is emerging evidence that it could play a role in modulating cognitive functioning during cerebral challenge. Given this and also evidence that APOE allele status can impact MS recovery and progression patterns, it is worth examining cerebral activation patterns in relation to APOE allele status to explore possible variable compensatory recruitment of neural resources (Burwick et al., 2006; Ghaffar et al., 2010). Considering what is currently known about the upregulation of activity associated with APOE- ϵ 4 in healthy controls, it is possible to better understand why cognitive deficits, in the absence of rigorous neuropsychological assessment, may go undetected during the early stages of MS if similar results are observed (Forn et al., 2007). Additionally, studying the relationship of MS and APOE genotypes can potentially improve understanding and highlight the clinical impact of genetic influence on the course and severity of disability in individuals with MS (Fazekas et al., 2001).

Study Goals

With these considerations in mind, the present study aims to examine cerebral activation in APOE- ϵ 4 positive and negative MS patients while they are performing the n-back working memory task. Based on the previous literature, it is hypothesized that, relative to the APOE- ϵ 4 negative MS group, the APOE- ϵ 4 positive group will exhibit increased cerebral activation in the medial frontal and parietal regions bilaterally and in the right dorsolateral prefrontal cortex (Wishart et al., 2006; Forn et al., 2007; Cader et al., 2006; Chiaravalloti et al., 2005). It will be important to determine that both genetic groups do not differ on neurocognitive performance

variables, to ensure that any differences in brain activation observed, if any, are not attributable to predetermined differences in cognitive dysfunction (Ghaffar et al., 2010).

Hypotheses

Hypothesis 1: APOE-ε4 carriers with MS will exhibit increased cerebral activation during the n-back working memory task, relative to their non-APOE-ε4 carrying counterparts.

Hypothesis 2: Increased activation in APOE-ε4 carriers with MS will be observed in medial frontal and parietal regions bilaterally and in the right dorsolateral prefrontal cortex.

Methods

Participants

The research sample consisted of 43 community-based adult patients with MS. An advertisement was placed in the Central Pennsylvania Chapter of the National Multiple Sclerosis Society MS Connection newsletter to recruit participants. If interested, potential participants were required to contact study personnel to complete a telephone screen to determine eligibility. Participants included in the present study were diagnosed with MS, clinically confirmed by board-certified neurologists using Polman et al. (2010) criteria. Exclusionary criteria included: (a) neurological disease or medical condition other than MS that could significantly affect cognition and motor function; (b) drug or alcohol abuse; (c) learning disability or attention-deficit/hyperactivity disorder; (d) visual or motor impairments that would substantially interfere with testing procedures; and/or (e) MS disease relapse or use of corticosteroids within four

weeks of assessment. Once determined eligible, participants were scheduled and brought in for neuropsychological testing, genetic buccal (cheek cell) sample, and an MRI scan, administered by graduate students, trained by a licensed clinical neuropsychologist. Each participant's level of disability was determined using a neurologist's or, in the case that a neurologist's evaluation was not available, self-report rating on the Kurtzke's Expanded Disability Status Scale (EDSS). Upon their participation, participants were compensated \$100 and given a neuropsychological evaluation report outlining their functional capabilities. The Pennsylvania State University's Institutional Review Board approved this study.

Neuropsychological Testing

Participants were administered a battery of neuropsychological tests that evaluated premorbid intelligence, executive functioning, processing speed, and memory. Standard scores for each variable were calculated for participants in the present study, using healthy controls recruited for a separate study as the normative reference sample. These standard scores were then used to examine equivalences on neuropsychological test variables between APOE- ϵ 4 and non-APOE- ϵ 4 patients with MS. Descriptions of the included tests are described below.

Intelligence:

Wechsler Test of Adult Reading (WTAR). The WTAR (The Psychological Corporation, 2001) evaluates pre-morbid intellectual functioning in individuals aged 16 to 89. The test consists of 50 irregularly spelled words presented on a word card to be pronounced by participants (Venegas & Clark, 2011). A standard score is derived from the raw score, characterized by the number of correct pronunciations (maximum score of 50), which is then

compared to demographic data based on the normative test sample to determine the Demographic Predicted Full-Scale IQ (FSIQ). The WTAR is particularly useful when assessing for the presence and/or extent of cognitive impairment as a result of a cerebral insult or the onset of a neurological disorder (Strauss et al., 2006). The WTAR has been shown to be a valid and reliable test of pre-morbid intelligence with a test-retest reliability of 0.92 to 0.94 in a United States sample, demonstrating little practice effects (The Psychological Corporation, 2001).

ShIPLEY Institute of Living Scale-2 (ShIPLEY-2). The ShIPLEY-2 is a measure of general intellectual functioning and an indicator of overall cognitive functioning or impairment (ShIPLEY, Gruber, Martin, & Klein, 2009). To measure crystallized intelligence, the 40-item Vocabulary scale was administered. This scale required the participants to choose the word that is a synonym for the target word for each item from four options. The Abstraction scale measures fluid ability by presenting 25-items prompting participants to complete abstract sequences using problem-solving problems. The sum of the Vocabulary and Abstraction scales create Composite score A, which was found to have high and strong reliability, ranging from 0.88 to 0.97, by Kaya, Delen, & Bulut, 2012.

Executive Functioning:

Paced Auditory Serial Addition Task (PASAT). The PASAT (Gronwall, 1977; Gronwall & Sampson, 1974) is a task of divided attention and working memory. This task requires the participant to listen to an auditory recording presenting 60 digits at a rate of one per two or three seconds. The current study focuses on performance of the PASAT presented at a rate of one per three seconds. The participant must listen and add each digit presented to the previously announced digit, beginning as soon as the recording says the first number. For example, if the recording presents the following sequence “3-8-5-1-7,” the correct responses are “11-13-6-8.”

According to a study conducted by Tombaugh (2006), the PASAT demonstrates strong psychometric properties, including a high degree of internal consistency and a test-retest reliability ranging from 0.90 to 0.97.

Controlled Oral Word Association Test (COWAT). The COWAT assesses phonemic verbal fluency. This measure includes three trials of naming words using a predetermined set of three letters (Benton and Hamsher, 1989; Lezak, 2012). The first form of the COWAT was used in the present study; therefore, the set of letters given was F-A-S. To administer this test, examinees are asked to say aloud as many words as they can in 60 seconds that begin with the letter “F,” excluding proper nouns, numbers, and the same word with a different suffix. The same process continues for the two subsequent letters. With a test-retest reliability of 0.73 and high internal consistency ($R = 0.83$), the COWAT is a valid measure for adults 16-70 years (Ruff, Light, & Parker, 1996). Alternative versions of this test can be administered to reduce practice effects (Lezak, 2012).

Animal Fluency. Similar to the COWAT, Animal Fluency is a verbal fluency task, specifically focusing on semantic fluency (Lezak, 2012). One trial is given in which participants are prompted to say aloud as many animals they can think of in a span of one minute. To avoid practice effects if re-administration is necessary, alternative forms with different categories exist. Both short and long intervals of the Animal Fluency test have a test-retest reliability of approximately 0.70 (Basso, Bornstein, & Lang, 1999; Dikmen, Heaton, Grant & Temkin, 1999; Harrison, Buxton, Husain, & Wise, 2000; Levine, Miller, Becker, Selnes, & Cohen, 2004, all as cited by Strauss et al., 2006).

Memory:

Brief Visuospatial Memory Test – Revised (BVMT-R). The BVMT-R (Benedict, 1997) is a pencil-and-paper task designed to measure visuospatial learning and memory. In three separate trials, the participant is presented with a stimulus sheet with six figures assembled in a 2 X 3 format for just 10 seconds. After each learning trial, the participant is asked to draw as many figures as they can remember as precisely as possible and in the correct location on the page. The participant is then prompted to draw the same figures from memory as accurately as possible in the correct location, after a 25-minute delay. While optional, a copy trial, which requires the participant to copy the geometric figures exactly how they are presented, was given to help identify visuoconstructive deficits that may impact overall task performance and to help scoring responses on the recall trials (Tam & Schmitter-Edgecombe, 2013). Overall, the BVMT-R is highly valid and reliable: the reliability coefficients for the three learning trials range from 0.96 to 0.97. The delayed recall trial reliability coefficient is 0.97 (Lezak, 2012).

California Verbal Learning Test-II (CVLT-II). The CVLT-II (Delis, Kramer, Kaplan, & Ober, 2000) is a verbal word-learning task designed to assess memory (Lezak, 2012). Word List A consists of 16 words and is presented to the participant at a rate of slightly slower than one word per second for five trials. The word list is broken down into four categories: furniture, vegetables, ways of traveling, and animals. Four items per category are included. After the words are presented in a randomized order, participants are instructed to recall the words in any order. While participants are not informed of the category composition of the word list provided, they are expected to semantically associate words of the same category as a strategy to learn and remember more of the words. As an interference trial, List B, consisting of four items from two overlapping categories in addition to eight words from two non-overlapping categories, is read to participants, who are then prompted to recall as many words as they can remember. Immediately

following the interference trial, short delay free recall and short delay cued recall trials are administered. In the short delayed free recall, participants are prompted to recall any word from the List A; participants are prompted to recall the items from each of the presented categories in the short delayed cued recall. Long delay free and cued recall trials are administered after a 20-minute delay. Then in the recognition trial, participants are orally presented with a list of 48 words, with items from both List A, List B, and unrelated words, and prompted to answer “yes” or “no” if the word was from List A. The CVLT-II has high reliability demonstrating a test-retest reliability ranging from 0.80 and 0.84 (Delis et al., 2000; Woods, Delis, Scott, Kramer, & Holdnack, 2006; Lezak, 2012).

Processing Speed:

Symbol Digit Modalities Test-Oral (SDMT). As a test of complex attention, visual tracking, and processing speed, the SDMT demonstrated a fairly high test-retest reliability (0.76) (Smith, 1982; Strauss, 2006; Lezak, 2012). To help control for motor-writing deficits, often observed in patients with MS, the oral version of the SDMT was administered in this study (Arnett et al., 1999). In this task, a sheet is given to participants, which includes a key followed by eight rows of two boxes stacked on top of the other. The key is made up of nine box pairs with each number (1-9) assigned to a different symbol. In the following rows consisting of 15 box pairs per row, a symbol appears in the top boxes while the boxes underneath remain blank. Examinees are prompted to match the symbol with the number according to the key presented at the top of the page. Participants have 90 seconds to say the correct symbol-number pairing aloud.

Psychosocial:

The Beck Depression Inventory – Fast Screen (BDI-FS). The BDI-FS is a 7-item self-report questionnaire developed to assess depressive symptoms, including dysphoria, anhedonia,

cognitive-related symptoms, and suicidal ideation in medical patients (Beck, Steer, & Brown, 2000). Given that the BDI-FS does not include the neurovegetative symptoms that often overlap with clinical signs and symptoms of MS, which are included in the Beck Depression Inventory-II, the BDI-FS is a highly valid measure when assessing MS and other clinical populations (Benedict, Fishman, McLellan, Bakshi, & Weinstock-Guttman, 2003; Strober & Arnett, 2015). Based on the extent to which participants agree with each statement that describes how they have been feeling the past two weeks, examinees rate each item on a scale of 0 to 3, where 0 indicates an absence of problems and 3 is the most severe level. For the item on Pessimism, for instance, 0 = I am not discouraged about my future, 3 = I feel my future is hopeless and will only get worse. The raw score is the sum of all of the selected statements chosen (Lezak, 2012).

Statistics

Descriptive statistics were used to evaluate the overall sample, using the calculated standard scores for each variable. Individuals with MS were independently divided into APOE- ϵ 4 positive and APOE- ϵ 4 negative groups, and independent sample *t*-tests were used to verify group equivalences across demographic and neuropsychological performance variables.

Magnetic Resonance Imaging

Behavioral Task. The *n*-back task is a well-established serial letter task, commonly administered during fMRI scans (Owen, McMillan, Laird, & Bullmore, 2005; Lezak, 2012). This behavioral task provides a measure of working memory. Prior to undergoing the fMRI, participants practiced a version of the *n*-back task, similar to the “zero-back” condition in Figure 1, to avoid

learning effects during the scanning session. During the fMRI scan itself, participants completed the 1- and 2-back conditions of the task (see Figure 1). In the 1-back condition, examinees were to respond if the current letter did or did not match the immediately preceding letter; whereas, in the 2-back task, participants were asked to respond if the letter did or did not match the letter presented two letters prior. Participants used left and right trigger buttons to respond to the task at hand while laying supine in the scanner

Blocks of 10 letters in white text on a black background were presented one at a time, while participants were in the scanner. Each letter was presented on the screen for 1750 milliseconds on the screen prior to a 250 ms inter-stimulus interval in which a black screen is presented. After each block of 10 trials, a white asterisk on a black background was visible to act as a rest period lasting 1400ms. Throughout the entire task, 8 blocks of 10 trials and 8 rest periods were presented in total. Mean reaction time and accuracy across all trials were the outcome measures from the task used for this study. Given that the *n*-back incorporates both a simple and more complex working memory tasks, this test is useful in demonstrating how neural activity responds to varying level of cognitive demands.

Figure 1: *N*-back Working Memory Task One- and Two-Back Conditions (derived Wishart et al., 2006).



MRI Data Acquisition. A 3-Tesla Siemens Magnetom Trio A Tim System was used to collect all MRI data. Before scanning, participants were informed of the importance of remaining completely still throughout the duration of the scanning session. To further stabilize the head within the coil as well as the rest of the body, Styrofoam pads were placed around the participant's body to reduce motion-induced signal degradation. High resolution structural T1-weighted MPRAGE images (1 mm isotropic resolution on 3T) were acquired to start each participant's scanning session and included the following parameters: 176 sagittal slices, repetition time (TR) 2530 ms, echo time (TE) 2.03, flip angle 7 degrees, field of view (FOV) 256 mm, voxel size = 1 x 1 x 1 mm³, acquisition time (TA) 6 minutes and 3 seconds.

In regards to functional magnetic resonance imaging (fMRI), scans were acquired using gradient echo-planar imaging for each participant with the following parameters: 50 sagittal slices, descending acquisition, thickness of 3 mm continuous, TR 2500 ms, TE 25ms, FOV 240 mm, flight angle 80 degrees, voxel size 3 x 3 x 3 mm.

Defining Brain Regions. The primary brain regions of interest in this study included the frontal and parietal lobes. Given the variability in Brodmann's areas across individuals and the overlap of these areas within brain regions, the dorsolateral prefrontal cortex (DLPFC) was defined by Hillary et al. (2003) as any area listed in the Talairach Daemon as "middle frontal," "medial frontal," or "superior frontal" activation. Therefore, for the purposes of this study, the following Brodmann's areas, or portions of Brodmann's areas, were considered a part of the DLPFC: 6, 8, 9, 10, 11, 32, and 46.

Functional Imaging Preprocessing. CONN was used to preprocess the fMRI data with the default standard preprocessing pipeline (Whitfield-Gabrieli & Nieto-Castanon, 2012; <https://www.nitrc.org/projects/conn>). Through the standard slice-timing algorithm in CONN,

time-series were corrected to account for signal differences between each volume. The data were spatially realigned to adjust for movement between slices. The standard Montreal Neurological Institute (MNI) space was applied to normalize the images by the resampling at 2 mm³ isotropic resolution. Data were spatially smoothed using a Gaussian kernel of full width half maximum (FWHM) 6 mm to improve signal to noise ratio.

FMRI Statistical Data Analysis. Using SPM8 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm/>), two-sample *t*-tests were conducted to test for hypothesized differences in brain activity as a function of APOE genotype in the 1- and 2-back conditions. APOE group (APOE-ε4 positive versus APOE-ε4 negative) was the independent variable and task-related signal change at each voxel was the dependent variable. In other words, cerebral activation in the APOE-ε4 positive group was contrasted with activation in the APOE-ε4 negative group in both the 1- and 2-back conditions of the n-back task. This differential contrast made viewing increased activation in certain regions in the APOE-ε4 positive group, relative to the non-APOE-ε4 group possible. Also examined was the reverse contrast (APOE-ε4 negative > APOE-ε4 positive) in both the 1- and 2-back conditions as well. As seen in previous functional analyses (Sweet, Rao, Primeau, Dugierian, & Cohen, 2006; Wishart et al., 2004), this study used uncorrected $p = .001$ levels as it is considered to provide protection against false positive results if there are clear hypotheses to location of findings (Forn et al., 2007). A cluster extent threshold of 30 voxels in combination with $p = .001$ were used in order to identify differential contrasts among APOE groups. The resulting MNI coordinates were inserted and compared to the Talairach Daemon Atlas included in FSL to determine each corresponding Brodman's area (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>).

Genetics

Using materials and methods suggested in Freeman et al. (2003), buccal samples were collected from each participant. DNA extraction and genotyping was performed in the Genomics Core Facility at The Pennsylvania State University, University Park. Two Taqman® Single Nucleotide Polymorphism (SNP) assays for SNPs APOE 112 (rs429358) and APOE158 (rs7412) were used to determine the APOE genotype for each participant, using the guidelines outlined by Christensen et al. (2008) and Ingelsson et al. (2003). The final genotypes could present as any homozygous or heterozygous pairs of $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles.

Results

Participant Demographic Characteristics

The overall sample ($N = 41$) was composed of 12 men and 29 females with a mean age of 51.98 ($SD = 11.7$) and a mean education level of 15.0 ($SD = 1.79$). When the sample as a whole was considered, 31.7% were APOE- $\epsilon 4$ carriers. A chi-square analysis was conducted to determine the presence of APOE- $\epsilon 4$ genotype status between the sexes. Results showed that there was no significant difference between the APOE- $\epsilon 4$ allele groups with respect to the proportion of male and female participants, $\chi^2(1, N = 41) = 0.21, p = 0.89$. An independent samples t -test was used to compare age, education, and disability status across the two APOE genotype groups. No significant differences in level of disability nor education between the APOE- $\epsilon 4$ and non-APOE- $\epsilon 4$ groups were identified. However, age between groups trended

towards significance $t(39) = 1.84$, $p = 0.074$. Demographic characteristics of participants are displayed according to their APOE allele status in Table 1.

Table 1 MS Sample Characteristics in APOE Allele Groups

Demographic Variables	Positive $\epsilon 4$ allele group (n = 13)				Negative $\epsilon 4$ allele group (n = 28)				p
	M	SD	N	%	M	SD	N	%	
Age (years)	56.77	12.22			49.75	10.99			.074*
Education (years)	14.69	1.97			15.14	1.72			.460
EDSS	4.19	1.68			4.18	1.67			.981
Sex									
Male			4	30.8	8		28.6		
Female			9	69.2	20		71.4		

*Approached significance at $p < .10$.

Neuropsychological Variables in APOE- $\epsilon 4$ + and $\epsilon 4$ - Patients with MS

After calculating standard scores for each outcome variable, independent samples t -tests were used to compare neurocognitive performance as a function of APOE- $\epsilon 4$ status. No significant differences in performance on measures of intelligence, processing speed, and verbal and visual memory were observed among MS patients with and without the APOE- $\epsilon 4$ genotype ($p > 0.05$). Additionally, APOE- $\epsilon 4$ groups did not significantly differ in reporting symptoms of depression. Trial 3 of the COWAT trended towards statistical significance, $t(30) = -1.789$, $p = 0.081$. Independent t -test results for each neuropsychological performance measure are presented in Table 2.

Brain Activation Results

APOE- $\epsilon 4$ carriers with MS and their non- APOE- $\epsilon 4$ counterparts with MS did not differ in terms of brain activation during the 1-back task. The reverse contrast (APOE- $\epsilon 4$ negative > APOE- $\epsilon 4$ positive) was also examined and did not present any differential activation.

The two-sample *t*-test ($p = .001$, uncorrected) revealed that during the 2-back task, APOE- $\epsilon 4$ positive individuals with MS, relative to APOE- $\epsilon 4$ negative individuals with MS, displayed increased activation in the right superior frontal gyrus (Brodmann's area 6) and the medial frontal gyri bilaterally (Brodmann's area 6, 8; Figure 2, Table 3). Again, the reverse contrast was compared for the 2-back condition. There were no regions in the APOE- $\epsilon 4$ negative group that showed greater activation than the APOE- $\epsilon 4$ positive group during the 2-back task.

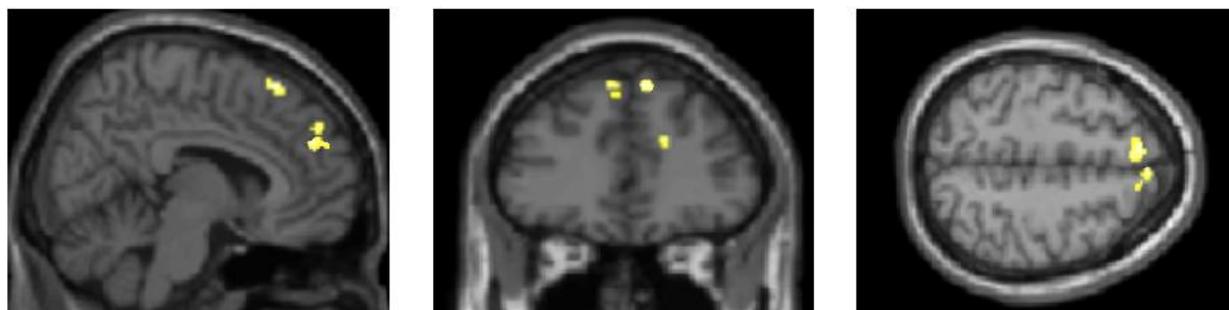
Table 2 APOE Group Equivalences on Neuropsychological Performance

Neuropsychological Variables	Positive $\epsilon 4$ allele group (n = 13)		Negative $\epsilon 4$ allele group (n = 28)		<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
WTAR					
Demographic Predicted FSIQ	107.25	7.98	109.79	7.22	0.33
Shipley					
Vocabulary	32.23	5.86	33.04	3.89	0.60
Abstraction	13.08	3.43	13.71	3.02	0.55
SDMT (oral)					
Total Correct	48.58	11.89	49.07	10.50	0.90
COWAT					
COWA 1	14.38	4.89	16.54	5.06	0.21
COWA 2	12.46	5.29	13.25	4.63	0.63
COWA 3	11.23	4.64	13.82	4.16	0.08*
Grand Total	38.08	12.70	43.61	12.10	0.19
Animal Naming					
Total	21.85	4.81	20.82	5.61	0.57
PASAT					
Total Correct	40.00	10.50	44.67	13.90	0.99
BVMT					
Total Recall	24.42	6.47	24.82	6.33	0.86
Delayed Recall	9.58	2.91	9.39	2.22	0.82
Percent Retained	91.33	19.30	93.53	12.10	0.66
Recognition Hits	5.75	0.45	5.57	0.69	0.34
CVLT-II					
Total Recall	50.38	10.50	47.18	12.30	0.42
Short Delay Recall	10.80	3.79	9.79	3.85	0.45
Long Delay Recall	10.69	3.33	10.36	3.76	0.79
Delayed Recognition	14.77	1.30	13.86	1.98	0.14
BDI-II	11.00	10.20	9.93	8.90	0.73

*Approached significance at $p < .10$.

Abbreviations: FSIQ = Full-scale Intelligence Quotient

Figure 2. Statistical Parametric Maps of Differential Contrasts in Brain Activation (APOE- ϵ 4 Positive > APOE- ϵ 4 Negative) during 2-back Condition^a



^a Increased cerebral activation in MS individuals with APOE- ϵ 4 genotype, relative to MS individuals without, in distributed frontal regions as expected for a working memory task. Images are shown in neurological convention at a threshold of $p = .001$. (See Table 3 and text for analyses and detailed description of the results).

Table 3. Activated Brain Regions during Working Memory (2-back task) in MS Individuals with and without the APOE- ϵ 4 Allele

Location of Voxel of Peak Effect	Montreal Neurological Institute (MNI) Coordinates			<i>t</i>
	<i>x</i>	<i>y</i>	<i>z</i>	
Right Superior Frontal Gyrus (Brodmann area 6)	10	26	60	4.68
Right Medial Frontal Gyrus (Brodmann area 8)	6	52	36	4.09
Left Medial Frontal Gyrus (Brodmann area 6)	-2	52	32	3.59

* $p < .001$, uncorrected

Discussion

The aim of the present study was to compare brain activation patterns associated with working memory as a function of APOE genotype status in a sample of individuals with MS. To ensure that any differential activation patterns observed were attributable to APOE status—not initial differences in neurocognitive functioning—demographic characteristics and neuropsychological performances of the APOE- ϵ 4 positive and APOE- ϵ 4 negative groups were compared (Ghaffar et al., 2010). These comparisons verified APOE group equivalences (APOE-

$\epsilon 4$ positive versus APOE- $\epsilon 4$ negative) on demographic variables and neuropsychological functioning.

The performance on the 2-back condition of the n-back working memory task in APOE- $\epsilon 4$ positive MS participants, relative to non-APOE- $\epsilon 4$ MS participants, was accompanied by increased activity in several cortical areas previously related to working memory (Boisgueheneuc et al., 2006; Forn et al., 2007). More specifically, APOE- $\epsilon 4$ positive MS participants showed increased activation in the right superior frontal gyrus (BA 6) and medial frontal gyri bilaterally (BA 6, 8) relative to MS participants without an $\epsilon 4$ allele. In other words, increased activation patterns were observed as predicted in the medial frontal regions bilaterally and the right DLPFC, as defined by Hillary et al. (2003; 2006) to include the superior frontal gyrus. In contrast, the APOE- $\epsilon 4$ positive group did not show any increased relative activation when compared to the APOE- $\epsilon 4$ negative group during the 1-back task.

Differences in brain activity were observed on the 2-back task, despite the fact that participants in both APOE genotype groups did not differ demographically or in terms of neurocognitive functioning. There were no areas in which APOE- $\epsilon 4$ negative individuals with MS demonstrated greater activation than APOE- $\epsilon 4$ positive individuals with MS on either the 1- and 2-back conditions. This may suggest that as memory load, and thus cognitive effort, increases from the 1-back to the 2-back, APOE- $\epsilon 4$ MS participants require a greater physiological and neural response to complete the task (Petrella, Lusting, Bucher, Jha, & Doraiswamy, 2002). These findings are consistent with prior fMRI research investigating the role of APOE in brain activation patterns observed in other clinical populations (Wishart et al., 2006; Bookheimer et al., 2000), in addition to individuals with MS relative to healthy controls (Forn et al., 2007; Sweet et al., 2004; Chiaravalloti et al., 2005; Cader et al., 2006; Hillary et al.,

2003; Staffen et al., 2002). In-scanner task performance should be compared in the future to ensure that resulting activation patterns are not attributed to initial differences in task performance.

The increased frontal lobe activation observed in the APOE- ϵ 4 positive MS group may reflect a compensatory mechanism of neural resources to help preserve cognition and facilitate completion of the task (Wishart et al. 2006; Forn et al., 2007; Staffen et al., 2002; Cader et al., 2006). The recruitment of the right prefrontal regions demonstrates a general response to diminished brain resources induced by a combination of the MS disease sequelae and inefficient neuronal processes linked to the APOE- ϵ 4 allele (Hillary et al., 2003; Ghaffar et al., 2010). Restructuring and reorganizing neural networks in addition to recruiting auxiliary brain regions enables the brain to attempt to functionally adapt in assisting brain regions compromised by MS and certain APOE genotypes, particular the ϵ 4 allele (Hillary et al., 2003; Chiaravalloti et al. 2007). If this neuronal plasticity via a compensatory mechanism is supported by further investigation, Wishart et al. (2006) suggested that once a critical threshold of brain pathology is met, due to a combination of MS and APOE genotype, additional activation may no longer be supported. This will result in the emergence of cognitive deficits. Future studies need to replicate this study and further investigate this mechanism to understand and determine the threshold that governs subsequent cognitive decline.

According to the right hemisphere novelty hypothesis proposed by Hillary et al. (2006), the increased recruitment of the right DLPFC in clinical populations is due to inefficient information processing, which then requires more resources to maintain cognitive control during working memory tasks—hence, the increased activation. In regards to the current study, a similar mechanism to accommodate for inefficiently processing the 2-back task stimuli may be at play in

the APOE- ϵ 4 positive group. For instance, the APOE- ϵ 4 MS group requires more cognitive control during the 2-back task to account for inefficient processing induced by the disruption of neural networks induced by MS and the APOE genotype condition. To maintain this control, this group may increase recruitment of the right DLPFC during cognitive tasks to initiate and develop subroutines to learn and complete the task, resulting in the observed increased activation. To support this hypothesis further, more examinations of activation during nonverbal, verbal and spatial working memory tasks are necessary, given that brain activation during these tasks may be dependent upon the material and task administered (Hillary et al., 2006).

Another possible explanation for the pattern of cerebral activation observed in the MS APOE- ϵ 4 carriers is task load or task difficulty (Hillary et al., 2003; Chiaravalloti et al., 2007). As memory load, and thus cognitive effort, increases in the 2-back task condition, auxiliary cerebral sources may be required to complete the task effectively. In healthy individuals (Manoach et al., 1997; Rympa & D'Esposito, 1999), in addition to a TBI population (Christodoulou et al. 2001), this relationship between working memory load and increased right frontal activation has been demonstrated. Given that the APOE- ϵ 4 positive group must functionally adapt to inefficient cognitive processing induced by both MS and ϵ 4 allele status in the present study, it is not surprising that MS APOE- ϵ 4 carriers required more resources, resulting in the upregulation of cerebral activity, to perform the working memory task, compared to the MS individuals without the ϵ 4 allele. Further exploration is needed to determine the source of this increased frontal lobe activation: permanent brain reorganization enabled by neuronal plasticity, functional adaptation to inefficient cognitive processing that occurs when the brain is impacted by MS or predisposed by the APOE- ϵ 4 allele, response to greater task difficulty or task load, or a combination of these possible explanations.

Despite offering useful information regarding the impact of MS and APOE genotype status on cerebral activation associated with working memory performance, this study is not without some methodological limitations. For example, it is important to note that the uncorrected p – value ($p = .001$) was used for the purposes of this study. When attempting to correct for multiple comparisons using familywise wise error (FWE) and false discovery rate (FDR) analyses, the significant results did not survive. Small sample size ($N = 41$) and size differentials in APOE groups limit the power of statistical tests used in this study. While differences are still observed using the uncorrected p – value, future research to replicate these findings is warranted for more detailed analyses with a larger sample and less differentials in groups. It is likely that with an increased number of participants, this trend noted in the frontal lobe comparison would most likely achieve statistical significance while also accounting for multiple comparison corrections.

Another potential limitation of this study is the way in which the APOE genotype groups were defined. Instead of comparing genetically homogeneous groups (e.g. $\epsilon 3/\epsilon 3$ versus $\epsilon 3/\epsilon 4$), this study used genetically heterogeneous groups: any MS participant with at least one $\epsilon 4$ allele was categorized as APOE- $\epsilon 4$ positive group, while those without any were in the APOE- $\epsilon 4$ negative group. This method of categorization does not take into account other rarer genotypes (i.e. $\epsilon 2/\epsilon 3$ or $\epsilon 2/\epsilon 4$) that could potentially influence findings (Wishart et al., 2006). Future studies should consider incorporating genetically homogeneous groups to account for potential confounds by including individuals with rarer genotypes.

Conclusion

In summary, individuals with MS who carry the APOE- ϵ 4 allele exhibited greater activation in frontal regions compared to individuals with MS without the APOE- ϵ 4 allele—a possible consequence of a compensatory mechanism to counter inefficient cognitive processing due to MS and APOE genotype status. A substantial amount of additional research further investigating the compensatory hypothesis is necessary to fully understand the implications of the results found in the current study. To understand the point at which brain activity may be increased, the mechanisms that lead to subsequent decline, and how this relates to the emergence of cognitive sequelae of MS, further research is needed (Wishart et al., 2006; Forn et al., 2007). If replicated with continued longitudinal research integrating neuropsychological assessment, genetics, and neuroimaging in MS samples, these findings could potentially improve understanding of the clinical impact of genetics on the course and severity of disability in MS (Fazekas et al., 2011).

References

- Arnett, P.A., Cadden, M., Roman, C.A.F., & Guty, E. (in press). Cognition and depression in multiple sclerosis. In B. Sandroff and J. DeLuca (Eds.), *Cognition and Behavior in Multiple Sclerosis*.
- Arnett, P.A., Higginson, C.I., Voss, W.D., Bender, W.I., Wurst, J.M., & Tippen, J.M. (1999). "Depression in multiple sclerosis: relationship to working memory capacity." *Neuropsychology*, 13(1), 546-556.
- Arnett, P.A. & Strober, L.B. (2014). Multiple sclerosis and demyelinating disorders. In M.W. Parsons and T.A. Hammeke (Eds.), *Clinical neuropsychology: A pocket handbook for assessment*. (pp. 287-307). Washington, D.C.: American Psychological Association.
- Beck, A.T., Steer, R.A., & Brown, G.K. (2000). BDI-Fast Screen for Medical Patients: Manual. San Antonio, TX: Psychological Corporation.
- Benton, A.I., & Hamsher, K. (1989). Multilingual Aphasia Examination. Iowa City, IA: AJA Associates.
- Benedict, R.H (1997). Brief Visuospatial Memory Test-Revised professional manual. Odessa, FL: Psychological Assessment Resources, Inc.
- Benedict, R.H., Fishman, I., McClellan, M.M., Bakshi, R., & Weinstock-Guttman, B. (2003). "Validity of the Beck Depression Inventory-Fast Screen in multiple sclerosis. [Validation Studies]. *Multiple Sclerosis*, 9(4), 393-396.

- Boisgueheneuc, F., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., ...Dubois, B. (2006). "Functions of the left superior frontal gyrus in humans: A lesion study." *Brain*, 129(12), 3315-3328.
- Bookheimer, S.Y., Strojwas, M.H., Cohen, M.S., Saunders, A.M., Pericak-Vance, M.A., Mazziotta, J.C., Small, G.W. (2000). "Patterns of brain activation in people at risk for Alzheimer's disease." *The New England Journal of Medicine*, 343(7), 450-456.
- Brassington, J.C. & Marsh, N.V. (1998). "Neuropsychological aspects of multiple sclerosis." *Neuropsychology Review*, 8(2), 43-77.
- Burwick, R.M., Ramsay, P.P., Haines, J.L., Hauser, S.L., Oksenberg, J.R., Pericak-Vance, M.A., ... Barcellos, L.F. (2006). "APOE epsilon variation in multiple sclerosis susceptibility and disease severity: Some answers." *Neurology*, 66(9), 1373-1383.
- Cader, S., Cifelli, A., Abu-Omar, Y., Palace, J., & Matthews, P.M. (2006). "Reduced brain functional reserve and altered functional connectivity in patients with multiple sclerosis." *Brain*, 129(2), 527-537.
- Chiaravalloti, N.D., Hillary, F.G., Ricker, J.H., Cristodoulou, C., Kalnin, A.J., ...DeLuca, J. (2005). "Cerebral activation patterns during working memory performance in multiple sclerosis using fMRI." *Journal of Clinical and Experimental Neuropsychology*, 27(1), 33-54.
- Christensen, H., Batterham, P.J., Mackinnon, A.J., Jorm, A.F., Mack, H.A., Mather, K.A., ...Eastel, S. (2008). "The association of APOE genotype and cognitive decline in interaction with risk factors in a 65-69 year old community sample." *BMC Geriatrics*, 8(14), 14-24.

- Delis, D.C., Kramer, J.H., Kaplan, E., & Ober, B.A. (2000). California Verbal Learning Test-Second Edition (CVLT-II). San Antonio, TX: Psychological Corporation.
- Dousset, V., Gayou, A., Brochet, B., & Iron, A. (1998). "ApoE polymorphism in multiple sclerosis. *Multiple Sclerosis*, 4, 357(abstract).
- Evangelou, N., Jackson, M., Beeson, D., & Palace J. (1999). "Association of the apoE epsilon 4 allele with disease activity in multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry*, 67(2), 203-205.
- Fazekas, F., Strasser-Fuchs, S., Kollegger, T., Berger, W., Krisoferitsch, H., Schmidt, C., ...Schmidt, R. (2001). "Apolipoprotein E ϵ 4 is associated with rapid progression of multiple sclerosis." *Neurology*, 57(5), 853-857.
- Forn, C., Barros-Loscertales, A., Escudero, J., Benlloch, V., Campos, S., Parcet M.A., & Ávila, C. (2007). "Compensatory activations in patients with multiple sclerosis during preserved performance on the auditory n-back task." *Human Brain Mapping*, 28(5), 424-430.
- Freeman, B., Smith, N., Curtis, C., Hockett, L., Mill, J., & Craig, L.W. (2003). "DNA from buccal swabs recruited by mail: Evaluation of storage effects on long-term stability and suitability for multiplex polymerase chain reaction genotyping. *Behavior Genetics*, 33(1), 67-72.
- Ghaffar, O., Reis, M., Pennell, N., O'Connor, P., & Feinstein, A. (2010). "APOE ϵ 4 and the cognitive genetics of multiple sclerosis." *Neurology*, 74(20), 1611-1618.
- Greenwood, P.M. & Parasuraman, R. (2003). "Normal genetic variation, cognition, and aging." *Behavioral and Cognitive Neuroscience Reviews*, 2(4), 278-306.
- Gronwall, D.M.A. (1997). "Paced Auditory Serial-Addition Task: A measure of recovery from concussion." *Perceptual and Motor Skills*, 44, 367-373.

- Gronwall, D.M.A. & Sampson, H. (1974). *The psychological effects of concussion*. Auckland, New Zealand: Auckland University Press.
- Hillary, F.G., Chiaravalloti, N.D., Ricker, J.H., Steffener, J., Bly, B.M., Lange, G., ...DeLuca, J. (2003). "An investigation of working memory rehearsal in multiple sclerosis using fMRI." *Journal of Clinical and Experimental Neuropsychology*, 25(7), 965-978.
- Hillary, F.G., Genova, H.M., Chiaravallati, N.D., Rympha, B., & DeLuca, J. (2006). "Prefrontal modulation of working memory performance in brain injury and disease." *Human Brain Mapping*, 27(11), 837-847.
- Hùgh, P, Otuari, A., Schreiber, K., Blinkenberg, M., Jurgensen, O.S., Ryder, L., ...Knudsen, G.M., (2000). "Apolipoprotein E and multiple sclerosis: Impact of the epsilon-4 allele on susceptibility, clinical type, and progression rate." *Multiple Sclerosis*, 6(4), 226-230.
- Ingelsson, M., Shin, Y., Irazarry, M.C., Hyman, B.T., Lilius, L., Forsell, C., & Graff, C. (2003). "Genotyping of apolipoprotein E: comparative evaluation of different protocols." *Current Protocols in Human Genetics*, 9(14, Suppl. 38), 1-13.
- Kaya, F., Delen, E., & Bulun, O. (2012). "Test Review: *Shipley-2 Manual*." *Journal of Psychoeducational Assessment*, 30(6), 593-597.
- Jenkinson, M., Beckmann, C.F., Behrens, T.E.J., Woolrich, M.W., & Smith, S.M. (2012). "FSL." *NeuroImage*, 62(2), 782-790.
- Mayeux, R. (2003). "Epidemiology of neurodegeneration." *Annual Review of Neuroscience*, 26, 81-104.
- Lezak, M.D., Howieson, D.B., Bigler, E.D., & Tranel, D. (2012). *Neuropsychological Assessment: 5th Edition*. New York, NY: Oxford University Press.

- National Multiple Sclerosis Society. (2017). MS Prevalence. Retrieved February 22, 2018, from <https://www.nationalmssociety.org/About-the-Society/MS-Prevalence>
- Owen, A.M., McMillan, K.M., Laird, A.R., & Bullmore, E. (2005). "N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies." *Human Brain Mapping, 25*(1), 46-59.
- Petrella, J.R., Lustig, C., Bucher, L.A., Jha, A.P., & Doraiswamy, P.M. (2002). "Prefrontal activation patterns in subjects at risk for Alzheimer disease." *The American Journal of Geriatric Psychiatry, 10*(1), 112-113.
- Polman, C., Reingold, S., Banwell, B., Clanet, M., Cohen, B.J., Filippi, M., ... Wolinsky, J.S. (2011). "Diagnostic criteria for multiple sclerosis: 2010 revision to the McDonald Criteria." *Annals of Neurology, 69*(2), 292-302.
- Rao, S.M. (1990). *Neurobehavioral aspects of multiple sclerosis*. New York: Oxford University Press.
- Ruff, R.M., Light, R.H., Parker, S.B. (1996). "Benton Controlled Oral Word Association Test: Reliability and updated norms." *Archives of Clinical Neuropsychology, 11*(4), 329-338.
- Rumrill, P.D., Kaleta, D.A., & Battersby, J.C. (1996). Etiology, incidence, and prevalence. In P.D. Rumrill (Ed.), *Employment issues and multiple sclerosis*. New York: Demos Vermade.
- Shipley, W.C., Gruber, C.P., Martin, T.A., & Klein, A.M. (2009). *Shipley-2*. Los Angeles, CA: Western Psychological Services.
- Smith, A. (1982). Symbol Digits Modalities Test. Los Angeles: Western Psychological Services.
- Staffen, W., Mair, A., Zauner, H., Unterrainer, J., Niederhofer, H., Kutzelnigg, A., ... Ladurner, G. (2002). "Cognitive function and fMRI in patients with multiple sclerosis:

- evidence for compensatory cortical activation during an attention task.” *Brain*, 125(6), 1275-1282.
- Strauss, E. Sherman, E., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary*. New York, NY: Oxford University Press.
- Strober, L.B. & Arnett, P.A. (2015). “Depression in multiple sclerosis: The utility of common self-report instruments and development of disease-specific measure.” *Journal of Clinical and Experimental Neuropsychology*, 7(7), 722-732.
- Sweet, L.H., Rao, S.M., Primeau, M., Durgerian, S., Cohen, R.A. (2004). “Functional magnetic resonance imaging response to increased verbal working memory demands among patients with multiple sclerosis.” *Human Brain Mapping*, 27(1), 28-36.
- Sweet, L.H., Rao, S.M., Primeau, M., Mayer, A.R., & Cohen, R.A. (2004). “Functional magnetic resonance imaging of working memory among multiple sclerosis patients.” *Journal of Neuroimaging*, 14(2), 150-157.
- Sylantiev, C., Chapman, J., & Chilkevich, O. (1998) “The apoE 4 allele and progression of disability in multiple sclerosis.” *Neurology*, 50(4): A150. Abstract.
- Tam, J.W. & Schmitter-Edgecombe, M. (2013). “The role of processing speed in the Brief Visuospatial Memory Test – Revised.” *Clinical Neuropsychology*, 27(6), 962-972.
- Teter, B., Xu, P.T., Gilbert, J.R., Roses, A.D., Galasko, D., & Cole, G.M. (2002). “Defective neuronal sprouting by human apolipoprotein E4 is a gain-of-negative function.” *Journal of Neuroscience Research*, 68(3), 331-336.
- The Psychological Corporation. (2001). *Wechsler Test of Adult Reading*. San Antonio, TX: Harcourt Assessment.

- Tombaugh, T.N. (2006). "A comprehensive review of the Paced Auditory Serial-Addition Test (PASAT). *Archives of Clinical Neuropsychology*, 21, 53-76.
- White, F., Nicoll, J.A., Roses, A.D., & Horsburgh, K. (2001). "Impaired neuronal plasticity in transgenic mice expressive human apolipoprotein E4 compared to E3 in a model of entorhinal cortex lesion." *Neurobiology of Disease*, 8(4), 611-625.
- Whitfield-Gabrieli, S. & Nieto-Castanon, A. (2012). "Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks." *Brain Connectivity*, 2(3), 125-141.
- Wishart, H.A., Saykin, A.J., McDonald, B.C., Mamourian, A.C., Flashman, L.A., Schuschu, K.R., ...Kasper, L.H. (2004). "Brain activation patterns associated with working memory in relapsing-remitting MS." *Neurology*, 62(2), 234-238.
- Wishart, H.A., Saykin, A.J., Rabin, L.A., Santulli, R.B., Flashman, L.A., Guerin, S.J., Mamourian, A.C., ...McAllister, T.W. (2006). "Increased brain activation during working memory in cognitively intact adults with the APOE ϵ 4 allele." *American Journal of Psychiatry*, 163(9), 1603-1610.
- Woods, S.P., Delis, D.C., Scott, J.C., Kramer, J.H, & Holdnack, J.A. (2006). "The California Verbal Learning Test – second edition: Test-retest reliability, practice effects, and reliable change indices for the standard and alternate forms." *Archives of Clinical Neuropsychology*, 21(5), 413-420.

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Education

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Thesis Supervisor: Peter A. Arnett, Ph.D.

University Park, PA

Graduation Spring 2018

Culture & Disability: Study Abroad, Dublin & Galway, Ireland

Summer 2017

Penn State faculty-led program. Engaged with multiple service-providing agencies for people with varying sensory, intellectual/cognitive, or physical disabilities across Dublin. Attended the 9th

International Disability Summer School, hosted by NUI Galway's Centre for Disability Law and Policy, with a focus on the UN Convention on the Rights of Persons with Disabilities.

Research Experience

Penn State Sports Concussion Research Lab, University Park, PA

Sept. 2014 – present

Research Assistant

Principal Investigator: Dr. Peter A. Arnett, Professor of Psychology, Penn State University

- Administer comprehensive neuropsychological test battery, which includes both paper-and pencil and computerized neurocognitive tests, to healthy controls collegiate student-athletes at baseline and post-concussion.
- Study coordinator for genetic and neuropsychological study of high school student-athletes; involved in recruitment, consenting, and coordinating the genetic/DNA collection of student-athletes from a local high school.
- Contacted, performed phone screens, and recruited healthy college students to participate in study focusing on performance on a concussion battery.
- Score, enter, and analyze data using SPSS; assist graduate students with research projects.

Neuropsychology of Multiple Sclerosis Research Lab, University Park, PA

Sept. 2017 – present

Research Assistant

Principal Investigator: Dr. Peter A. Arnett, Professor of Psychology, Penn State University

- Administer neuropsychological test battery to participants with multiple sclerosis and depression.
- Trained to run Siemens 3T MRI scans: operating console, monitoring safety, and collecting and analyzing data.

Publications & Book Chapters

Arnett, P.A., Guty, E., & **Bradson, M.L.** (in press). Assessment of Depression and Anxiety in Sports Concussion Evaluations. Chapter to appear in *Neuropsychological Perspectives on Sports-Related Concussion* (Peter Arnett, Ed.). American Psychological Association: Washington, DC.

Arnett, P.A., Guty, E., & **Bradson, M.L.** (2017). Assessment and Impact of Depression in Sports Concussion Evaluations. *NAN Bulletin*, 31(2), 18-20.

Merritt, V.C., **Bradson, M.L.**, Meyer, J.E., & Arnett, P.A. (2017). Evaluating the test-retest reliability of symptom indices associated with the ImPACT post-concussion symptom scale (PCSS). *Journal of Clinical and Experimental Neuropsychology*, 40(4), 377-388.

Abstract/Poster Presentations

Bradson, M.L., Roman, C.A.F., & Arnett, P.A. (2018, April). Cerebral Activation during working memory in multiple sclerosis with the APOE epsilon-4 allele. Poster presented at Penn State's Psi Chi Undergraduate Research Exhibition, University Park, PA.

Merritt, V.C., **Bradson, M.L.**, Meyer, J.E., & Arnett, P.A. (2017, February). Evaluating the test-retest reliability of symptom indices associated with the ImPACT post-concussion symptom scale (PCSS). Poster presented at International Neuropsychological Society, New Orleans, LA.

Merritt, V.C., **Bradson, M.L.**, Meyer, J.E., & Arnett, P.A. (2017, April). Evaluating the test-retest reliability of symptom indices associated with the ImPACT post-concussion symptom scale (PCSS). Poster presented at Penn State's Psi Chi Undergraduate Research Exhibition, University Park, PA.

Honors

The Pennsylvania State University, Graduate School in Psychology University Park, PA
Spring 2017

Invited by faculty to enroll in a course on Neuropsychological Assessment as part of the Clinical Psychology Graduate Training Program.

Paterno Fellows Program

Spring 2015 – present

Honors Program including advanced academic coursework, thesis, study abroad and/or internship, ethics, and leadership & service commitment.

Volunteer Experience

Penn State Service Immersion Trip, New Orleans, Louisiana

May 2016, May 2017

Volunteer, Student Facilitator

Served at a local food pantry. Partnered with Arc of Greater New Orleans to harvest and maintain local farm produce in addition to sorting and repackaging recycled Mardi Gras beads. Drained trash receptacles to minimize mosquito prevalence and prevent water-borne illnesses in the Lower 9th Ward.

Mission Trip, Managua, Nicaragua

Summer 2016

Volunteer

Partnered with Vida Joven de Nicaragua (Young Life) to perform community outreach activities, including painting murals, planting gardens, and cleaning local schools. Completed social enrichment activities with local children and families. Painted houses for persons with physical disabilities.

Awards

Costello Family Scholarship, Penn State, College of Liberal Arts, Dept. of Psychology (Spring 2018)

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Ready to Succeed Scholarship, Pennsylvania Higher Education Assistance Agency (2015-2017)

Goffberg Psychology Fund (Spring 2017)

Susan Welch Dean's Chair Scholarship, Penn State, College of Liberal Arts (Spring 2017)

Style Family Fund, Penn State's Paterno Fellows Program, College of Liberal Arts (Summer 2017)