THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

INTERCOLLEGE PROGRAM

VERBAL FLUENCY AND DTI IN MULTIPLE SCLEROSIS

KATHLEEN INSETTA
SPRING 2014

A thesis
submitted in partial fulfillment
of the requirements
for a baccalaureate degree
in Science
with honors in Neuroscience

Reviewed and approved* by the following:

Peter Arnett, Ph. D.
Professor of Psychology
Director of Clinical Training
Thesis Supervisor

Ping Li, Ph. D.
Professor of Psychology, Linguistics, and Information Sciences and Technology
Honors Adviser

* Signatures are on file in the Schreyer Honors College.

ABSTRACT

Verbal fluency is a common area of cognitive functioning studied in Multiple Sclerosis (MS); approximately 20-25% of MS patients experience verbal fluency deficits (Rao et al., 1991). The present study provides an examination of the relationship between verbal fluency and neural fiber tract integrity (as measured by Diffusion Tensor Imaging - DTI) in 31 MS patients. It may be that disruption in these fiber tracts underlies verbal fluency problems in these patients. Exploration of the relationship between verbal fluency and DTI score in MS patients helps to enhance our understanding of the factors that contribute to verbal fluency deficits in patients with MS. The Maximum Repetition Rate test (MRR), Controlled Oral Word Association task (COWAT), along with the Animal Naming test were used to measure verbal fluency. Magnetic Resonance Imaging (MRI) of the brain was conducted for the 31 MS participants and DTI score was derived. More specifically, the Apparent Diffusion Coefficient (ADC), Fractional Anisotropy (FA), and Relative Anisotropy (RA) were all used to measure the neural fiber integrity in the MS patients. It was hypothesized that all three verbal fluency measures would be correlated with DTI, with effect sizes varying between the three verbal fluency tests. More specifically, it was expected that the highest correlation would be found between the COWAT and DTI measures, as the COWAT is the most cognitively demanding of the three tasks. Pearson's correlations revealed that the MRR and COWAT were significantly correlated with DTI whereas the Animal Naming measure was not. This difference in correlation could be due to the greater cognitive demands required for the COWAT compared with the Animal Naming tasks, with these greater cognitive demands mediated by the need for greater neural fiber tract integrity. Additional implications of these findings are discussed.

TABLE OF CONTENTS

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to express my gratitude to Dr. Peter Arnett for his vital assistance in working with and analyzing the data. I would also like to thank Dede Ukueberuwa for her valuable comments and support throughout the process. Without their help and support, this project would not have been possible.

Introduction

First depicted as a strange neurological disorder in 1838, Multiple Sclerosis (MS) presently affects over 2.5 million people worldwide and is the most prevalent chronic disabling neurological disease among middle-aged adults in the US, impacting the lives of approximately 400,000 citizens (Prakash, 2008). In fact, a new person is diagnosed in the US approximately every hour (Nocentini et al., 2012, p. v). Because of its prevalence, understanding the underlying mechanisms contributing to various symptoms such cognitive problems involving verbal fluency deficits is valuable information in the clinical world of neuroscience.

MS is a chronic demyelinating and degenerative disease of the central nervous system (CNS) with the potential to express a variety of functional impairments and disabilities (Nocentini et al., 2012, p. 3). The symptoms result from the interference of smooth and rapid conduction of electrical potentials along neuronal pathways in the CNS due to demyelination and transection of nerve fibers in the brain, brain stem, spinal cord, and optic nerves (Prakash, 2008).

The clinical characteristics of MS in terms of onset of disease, as well as evolution of the course, are greatly variable among patients. The typical factors that classify the disease are course, clinical symptoms, signs, and location of lesions. There are four subtypes of MS, which include relapsing-remitting, secondary progressive, primary progressive and progressive-relapsing course types.

Nocentini et al. (2012, p. 11) provide a thorough definition of all four types. In order to classify the types, it is important to know the definition of a “relapse” as an acute development of new symptoms, objective signs of neurological dysfunctions, or reappearance of preexisting symptoms lasting longer than 24 hours. The first type, relapsing-remitting MS (RRMS), is the most common and makes up approximately half of all cases. RRMS consists of relapses followed by recovery of functions, with a stable course and lack of progression between relapses. Secondary progressive MS (SPMS) occurs after the relapsing-remitting form and is a progression of neurological deficits with rare improvement. The third classification, primary progressive MS (PPMS), is progression of the disease from onset and has rare periods of stability and temporary improvements. Lastly, progressive-relapsing MS (PRMS) is also progressive from onset and is different from PPMS in the sense that it also has clear acute relapses. In this study, the subjects were limited to two course types: Relapse-Remitting, and Secondary Progressive, thus eliminating additional factors affiliated with the other two course types.

When diagnosing a neurological condition such as MS, Magnetic Resonance Imaging (MRI) is very useful in the sense that it offers high-resolution, noninvasive, in vivo imaging without radiation exposure (Rodriguez et al., 2013, p. 47). MRI provides structural and functional information that has revolutionized the diagnosis and management of MS. Diffusion Tensor Imaging (DTI) is a type of MRI that is utilized in the present study. According to Rodriguez et al. (2013, p. 61), DTI provides insight into the "degrees of freedom" of molecular water movement and provides information on tissue integrity and "diffusion directionality." DTI is used to achieve detailed tractography of directional predominance of water movements.

Dong et al. (2004), explain the concepts behind DTI. In brain tissue, barriers placed by structures such as myelin sheaths, cell membranes, and white matter tracts reduce water diffusion. Thus, the diffusion of water molecules is less restricted along the long-axis of a group of aligned tissue fibers as opposed to perpendicular to the axis. The condition of directionally dependent diffusion in the brain is termed "anisotropic." Three measures are used to portray tissue diffusion properties as listed by Dong et al. (2004). First, the apparent diffusion coefficient (ADC) provides information on the degree of restriction of water molecules. Second, fractional anisotropy (FA) is the degree of directionality. For example, white matter is a highly directional axonal fiber that appears hyperintense on an FA map. Third, predominant diffusion direction is used as an input to fiber tracking algorithms. In the present study in particular, relative anisotropy (RA) is used, and is derived from a ratio of the anisotropic portion of the diffusion tensor to the isotropic portion (Dong et al. 2004). As a whole, the more unrestricted the water molecules are in a given tissue, the higher the ADC will be and the lower the anisotropy values, FA and RA.

In application to MS, DTI is used to detect and quantify related tissue damage within and outside T2-visible lesions. Rovaris et al. (2008) wrote a paper studying DTI techniques in application to the study of MS and determined that DTI is sensitive to the evolution of damage in the brain due to MS over time and provides in vivo correlates of MS clinical severity and paraclinical markers of long-term disease evolution. ADC values in MS patients are consistently reported to be increased within both T2-visible lesions and the normal-appearing white matter due to pathological processes that decrease the number of restricting barriers.

Verbal fluency is one example of a clinical marker in patients with MS. Previous studies have confirmed verbal fluency deficits in MS. Arnett et. al (2006) found comparable phonemic and semantic fluency deficits in MS patients. Interestingly enough, phonemic and semantic fluency deficits were strongly correlated with neurological disability indexed by the Expanded Disability Status Scale (EDSS). The study as a whole concluded that measures of fluency and cognitive speed were some of the most sensitive markers of cognitive impairment in MS and that both phonemic and semantic fluency deficits were greater for patients with more neurological disability and chronic progressive course type.

The present study evaluated the relationship between DTI in MS patients and their performance on three different verbal fluency tasks. More specifically, DTI was used to examine the relationship between ADC, FA, and RA values and three verbal fluency tasks including the MRR, COWAT, and Animal Naming in MS patients. Because the three verbal fluency tasks are qualitatively different, it is essential to consider the different magnitude of deficits that may occur between the rudimentary, phonemic, and semantic verbal fluency tasks of the MRR, COWAT, and Animal naming, respectively, and how this difference may be correlated to the DTI measures. Data from Henry et al. in 2006 shows that MS patients are substantially but similarly impaired on phonemic and semantic fluency tests. The study also found that deficits in semantic and phonemic verbal fluency were proportional to the deficits on the Symbol Digit Modalities Test (SMDT), suggesting that phonemic and semantic verbal fluency deficits in MS may not be particularly associated with executive function, but rather with cognitive slowing (Henry et al., 2006).

It was hypothesized in the present study that disruption of fiber tracts underlies verbal fluency problems; thus, increased ADC and decreased FA and RA should be associated with verbal fluency problems in patients with MS. Furthermore, it was expected that there would be a greater correlation between demanding tasks such as the phonemic COWAT, as compared to the more rudimentary MRR measures. Specifically it was expected that the more cognitively demanding verbal fluency tasks (i.e., COWAT involving letter-word fluency) would be more highly associated with DTI markers of fiber tract integrity than less demanding fluency tasks (i.e., Animal Naming test involving category naming), and that there would be minimal correlation between the DTI indices and the more rudimentary MRR task.

Methods

Participants

All 31 participants were part of a larger, longitudinal study of MS at The Pennsylvania State University. The office of Research Protections and Institutional Review Board approved the longitudinal study and it is funded by a grant through the National Multiple Sclerosis Society. Subjects were excluded from this specific study for incomplete data for the variables examined: age, gender, education, EDSS, course type, and diagnosis duration. In total, there were 8 males and 23 females included in this study. The data were dichotomized and patients with the course type of either Relapsing-Remitting (RR) or Secondary Progressive (SP) were included: 21 RR and 10 SP. A summary of the characteristics can be found in Table 1 below. The verbal fluency tasks, along with the MRI, were conducted on the same day. A battery of questionnaires and neuropsychological measures were also performed in the presence of a researcher.

Descriptive Statistics			
	N	**Mean**	**Std. Deviation**
Age	31	52.45	11.07
EDUCATION (years)	31	14.52	1.73
DIAGNOSIS DURATION (years)	31	17.15	9.20
EDSS	31	4.00	1.78

Table 1. Descriptive Statistics of N = 31 Subjects

Psychometric Measures

Maximum Repetition Rate of Syllables and Multisyllabic Combinations (MRR; Kent et al., 1987)

The MRR is commonly used task that measures rudimentary oral motor speed. It requires participants to repeat three syllables, "pa", "ta", and "ka" as quickly as possible in one breath. Data for these three tasks were combined and the mean syllables per second was derived. After the three trials, a final trial required the repetition of "pa-ta-ka" in sequence. For this study, data from the final trial was used and quantified as mean phones per second.

Controlled Oral Word Association Task (COWAT; Benton & Hamsher, 1976)

The COWAT is a phonemic measure of verbal fluency that involves rapidly naming items that begin with a particular letter provided by the administrator. Participants were asked to generate as many words as possible that begin with the letter P, R, and W in 1-minute intervals. The total score equals the sum of the number of correct words generated by each participant in all three categories, P, R, and W.

Animal Naming Test (Strauss et al., 2006)

The Animal Naming Test measures verbal fluency using a semantic cue. Participants must name as many animals as possible in one minute. The dependent measure is the total number of animal words generated.

Expanded Disability Status Scale (EDSS; Kurtzke, 1983)

The Expanded Disability Status Scale (EDSS) quantifies disability in MS patients and monitors changes in the level of disability over time. The scale ranges from 0-10 in 0.5 unit increments that represent higher levels of disability. The steps are based on measures of impairment in eight functional systems including pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other.

Magnetic Resonance Imaging

The DTI score was derived using MedINRIA, an image viewing software. This software was developed within the Asceplios Research Project and provides clinicians with state-of-the-art algorithms dedicated to medical image processing and visualization (Deriche et. al, 2009). More specifically, the DTI Track module provides tools for in-deep DT-MRI analysis and fiber tracking including the FA, ADC, and RA computations used in this study.

Data Analytic Strategy

SPSS, a statistical analysis software, was used to determine significant correlation between the verbal fluency tasks and DTI score. Bivariate correlation was performed and the Pearson Correlation and Significance (2-tailed) values were measured between the three verbal fluency tasks and the three DTI measures.

Results

A Bivariate Correlation test was run for the three DTI measures and the three verbal fluency tasks. The Descriptive Statistics measures are found in Table 2, displaying the mean, standard deviation (SD), and the number of observations (N) for the six variables (Table 2).

Descriptive Statistics

	Mean	Std. Deviation	N
MRR pa-ta-ka combined, hones per sec	4.77	1.22	31
COWAT, GRAND TOTAL (P-R-W)	42.00	11.71	31
ANIMAL NAMING, TOTAL SCORE	21.35	4.10	31
Whole Brain DTI, FA Mean	.32	.01	31
Whole Brain DTI, ADC mean	3.29	.20	31
Whole Brain DTI, RA mean	.26	.01	31

Table 2. Descriptive Statistics of Variables of Interest

The Pearson's correlation test was used to measure the linear dependence between the variables. Table 3 exhibits the Pearson Correlation and Sig (2-tailed) values. In respect to the correlation values between verbal fluency and DTI, both FA and RA were positively correlated with the verbal fluency tasks and ADC was negatively correlated. The asterisks denote correlation significance ($p < .05$) between the variables. MRR was correlated significantly with FA mean and ADC mean ($r = .37$, and $r = -.43$, respectively). Next, COWAT was correlated with FA mean and RA mean ($r = .39$ and $r = .41$, respectively). Finally, Animal Naming showed no significant correlation with any of the DTI measures.

Correlations

		MRR pa-ta-ka combined, phones per sec	COWAT, GRAND TOTAL (P-R-W)	COWAT, CATEGORY: ANIMAL NAMING, TOTAL SCORE	Whole Brain DTI, FA Mean	Whole Brain DTI, ADC mean	Whole Brain DTI, RA mean
MRR pa-ta-ka combined, phones per sec	Pearson Correlation	1	.16	.21	.37*	-.43*	.15
	Sig. (2-tailed)		ns	ns	.04	.02	ns
	N	31	31	31	31	31	31
COWAT, GRAND TOTAL (P-R-W)	Pearson Correlation	.16	1	.42*	.39*	-.20	.41*
	Sig. (2-tailed)	.39		.02	.03	ns	.02
	N	31	31	31	31	31	31
ANIMAL NAMING, TOTAL SCORE	Pearson Correlation	.21	.42*	1	.25	-.28	.16
	Sig. (2-tailed)	.27	.02		ns	ns	ns
	N	31	31	31	31	31	31
Whole Brain DTI, FA Mean	Pearson Correlation	.37*	.39*	.25	1	-.73**	.86**
	Sig. (2-tailed)	.04	.03	ns		.00	.00
	N	31	31	31	31	31	31
Whole Brain DTI, ADC mean	Pearson Correlation	-.43*	-.20	-.28	-.73**	1	-.31
	Sig. (2-tailed)	.02	.27	ns	.00		ns
	N	31	31	31	31	31	31
Whole Brain DTI, RA mean	Pearson Correlation	.15	.41*	.16	.86**	-.31	1
	Sig. (2-tailed)	.41	.02	ns	.00	ns	
	N	31	31	31	31	31	31

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table 3. Correlation Values

Discussion

The results of this study show that performance on some verbal fluency tasks in individuals with MS is directly correlated with white matter fiber tract integrity. More specifically, the MRR and COWAT tasks are significantly correlated with DTI measures whereas Animal Naming is not. The results are discussed in further detail below.

When analyzing the DTI measures, this discussion will focus on FA and ADC measures because they provided the most consistently significant correlations. RA showed similar correlations as FA, so it will be excluded from the discussion for the sake of simplicity. As expected, the FA and ADC had correlations in opposite directions with FA correlations being positive with the verbal fluency measures, and ADC being negative. To review the meaning of these two DTI measures, a larger FA and a smaller ADC indicates greater brain integrity. Essentially, the more positive the FA value and the more negative the ADC value, the less fiber tract damage in the participant's white matter. To properly analyze the data, we will discuss MRR, COWAT, and Animal Naming separately.

First, the MRR task was found to be significantly correlated with FA ($r = .37$) and ADC ($r = -.43$). MRR was positively correlated with FA, indicating that as the FA value increased, the participant produced more phonemes per second. Thus, the greater the white matter integrity, the quicker the participants produced the syllables. This is similarly pictured when considering ADC, because the more negative the ADC value, the greater the white matter integrity. Thus, the number of phonemes a subject spoke per second in MRR was directly associated with greater fiber tract integrity.

Next, the COWAT was also significantly correlated with FA ($r = .39$). This indicates that the greater the white matter integrity, the greater the total number of words spoken in the phonemic task for the three categories, P, R, and W, combined. The COWAT was not significantly correlated with ADC. The ADC value was still negative, however (r = -.20), indicating that the trend between fluency and integrity was similar to FA, though it was not statistically significant.

Lastly, the Animal Naming task did not reach statistical significance with any of the DTI correlations. However, the trends were still promising, with FA (r = .25) and ADC (r = -.28) being positive and negative, respectively, indicating again that, as the fiber integrity decreased, the number of animal names recited per minute declined. The fact that the values did not reach statistical significance for this task could suggest that semantic fluency deficits are not as sensitive to fiber tract integrity (as measured by DTI) as the other fluency measures.

In conclusion, the MRR and COWAT verbal fluency tasks are related to fiber tract integrity in MS. The original hypothesis was that the COWAT would be most correlated with the DTI score and MRR would be the least, but the results were not consistent with this hypothesis. The Animal Naming task was unexpectedly an outlier with its correlations not being significant with DTI measures, while the other tasks, MRR and COWAT, were significantly correlated with DTI. A possible explanation of this discrepancy, at least between the significant correlation of the COWAT and the non-significant correlations with Animal Naming task, is that the semantic nature of Animal Naming makes it less cognitively demanding and therefore dependent on fewer brain resources to perform adequately. As for the MRR task, it is unclear why it had the highest correlations with DTI measures, but this suggests that it required the greatest brain integrity to perform. It may be that, given the rudimentary speech problems common in MS, for individuals with MS what appears to be a simple speech repetition task is actually very demanding and requires more than expected brain resources. Future research examining these correlations in a non-MS sample could lend some clarity to these findings. Taken together, this study provided some interesting findings relating to verbal fluency and white matter fiber tract integrity in patients with MS.

BIBLIOGRAPHY

Arnett, PA, Smith, MM, Berwick, FH, Benedict, RH, & Ahlstrom, BP (2008). Oral motor slowing in multiple sclerosis: relationship to neuropsychological tasks requiring an oral response. *Journal of International Neuropsychological Society.*

Benton A.L. & Hamsher, K.deS. (1989). *Multilingual Aphasia Examination.* Iowa City, IA: AJA Associates.

Deriche, R., Descoteaux, M., Fillar, P., Toussaint, N., Souplet, J.C. (2009) MedINRIA: Asclepios Research Team (Version 1.9.0). [Software]. Available from http://www sop.inria.fr/asclepios/software/MedINRIA/index.php.

Dong, Q., Welsh, R.C., Chenevert, T. L., Carlos, R.C., Maly-Sundgren, P., Gomez-Hassan, D.M., Mukherji, S. K., (2004). Clinical Applications of Diffusion Tensor Imaging. *Journal of Magnetic Resonance Imaging*, *19*, 6-18.

Henry, J.D. & Beatty, W.W. (2006). Verbal fluency deficits in multiple sclerosis. *Neuropsychologia, 44,* 1166-1174.

Kent, R.D., Kent, J.F., & Rosenbeck, J.C. (1987). Maximum performance tests of speech production. *Journal of Speech and Hearing Disorders, 52, 367-368.*

Kurtzke, J.F. (1983). Rating neurologic impairment in multiple sclerosis: An Expanded Disability Status Scale (EDSS). *Neurology, 33,* 1444-1452.

Nocentini, U., Caltagirone, C., Tedeschi, G. (2012). *Neuropsychiatric Dysfunction in Multiple Sclerosis*. Italy: Springer.

Prakash, RS, Snook EM, Motl RW, & Kramer, AF. (2008). Cognitive impairments in relapsing-remitting multiple sclerosis: a meta-analysis. *Sage Journals.*

Rao, S.M., Leo, G.J., Bernadin, L. et al (1991) Cognitive dysfunction in multiple sclerosis. *Neurology, 41* (5)*,* 685-691.

Rodriguez, M., Katarci, O., & Pirko, I. (2013*). Multiple Sclerosis*. New York: Amy Foundation for Medical Education and Research.

Rovaris, M., Agosta, F. Pagani, E. & Filippi, M. (2008). Multiple Sclerosis, Part I Nonconventional MRI Techniques Diffusion Tensor MR Imaging. *Neuroimaging Clinical of North America.*

Strauss, E., Sherman, E.M.S., & Spreen, O. (2006). *A compendenium of neuropsychological tests* (3rd ed.). New York, NY: Oxford University Press.

ACADEMIC VITA

Kathleen Insetta
418 E. College Ave., Apt 23
State College, PA 16801
kli5028@psu.edu

Education

Schreyer Honors College, The Pennsylvania State University
B.S. Science: Biological Sciences and Health Professions, Honors in Neuroscience
Eberly College of Science, Dean's List

Research Experience

The Pennsylvania State University, University Park, PA
Clinical Neuropsychology Lab at Penn State
Undergraduate Research Assistant, MS Longitudinal Study
- Investigate the relationship between DTI score and verbal fluency in subjects with MS
- Process data, assist with subject questionnaires, and formulate new research hypotheses

Clinical Work Experience

Bryn Mawr Rehab Hospital, Malvern, PA
Occupational and Physical Therapy Department
Therapy Aide
- Assist with transfers, take vitals, and lead exercises
- Work alongside occupational and physical therapists to provide appropriate treatment

Global Medical Brigades: Panama and Nicaragua
Student Volunteer, Treasurer
- Collaborated with physicians, PAs, NPs, dentists, and pharmacists to provide medical attention to underserved communities in Panama and Nicaragua
- Responsible for over $15,000 and its allotment for purchase of medicine and medical equipment

Other Activities

Tutor—Mid-State Literacy Council
Grader & Proctor—Organic Chemistry, Pennsylvania State University
Tour Guide—Penn State Lion Scouts
Mentor—Schreyer Honors College Orientation
Volunteer—Penn State Dance Marathon, Hospitality committee