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Editor's Corner

Peter Arnett, Ph.D.,
NAN Bulletin Editor

I am pleased to take on the Editorship of the NAN Bulletin! Although I primarily do research in academia at Penn State, my work has always had an eye squarely on application to clinical practice. I regularly supervise the students in our doctoral program in clinical psychology on neuropsychological assessments, and also continue to see patients in clinical practice. With this issue of the NAN Bulletin, the focus is on multiple sclerosis (MS). This common neurological disorder has been intensively studied by neuropsychologists and much has been learned about assessment and treatment of these patients to improve their quality of life. In the Professional Issues section, five experts in the field address core issues of interest in MS to practitioners including medication adherence, cognitive reserve, driving, physical activity, and fatigue. To enhance translation of the research reviewed to clinical practice, each article includes several clinical take home points.

The Patient Corner section of the Bulletin includes numerous practical resources that can be used by practitioners and patients alike in understanding and managing symptoms more effectively. In the Journal Section, a frequently downloaded article recently published in Archives of Clinical Neuropsychology, is reviewed that examines the relationship between depression symptoms and cognitive functioning in MS. Finally, the Student Corner includes two short pieces written by doctoral students training in clinical neuropsychology that discuss volunteer opportunities available to students in NAN, as well as things for students to do at a typical NAN conference.

Of note, with the next issue of the NAN Bulletin, I will be joined by an Associate Editor, Dr. John Randolph. Dr. Randolph is a true scientist-practitioner, working in private practice, conducting research in his role as adjunct assistant professor of psychiatry at the Geisel School of Medicine at Dartmouth College, and having recently edited a volume on Positive Neuropsychology. Finally, special thanks to Dr. Phil Fastenau, chair of the NAN Publications Committee, for his help and guidance with this issue.

Peter Arnett, Ph.D.,
Professor & Director of Clinical Training at Penn State University
NAN Bulletin Editor

Opinions expressed by the authors and advertisers do not necessarily reflect the position of the National Academy of Neuropsychology.

Clinical Research Grants Program

NAN is committed to the professional and scientific development of clinical neuropsychology. The mission of the Clinical Research Grants Program is to support meritorious small grants, pilot projects, or seed grants that address the value, worth, or efficacy of clinical neuropsychological assessment or interventions. These projects might be overlooked by traditional granting agencies because of their applied clinical nature or stage of development.

Instructions for Completing NAN Grant Application:

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Patient Corner

The National Multiple Sclerosis Society (NMSS) has a number of resources for helping individuals live better with MS. What follows are links for addressing some of the issues raised in this issue of the NAN Bulletin.

- **Tips for exercise in MS:**
http://www.nationalmssociety.org/NationalMSSociety/media/MS-NationalFiles/Brochures/Brochure-Exercise-as-Part-of-Everyday-Life.pdf

- **Understanding and managing fatigue in MS:**
http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Brochure-Fatigue-What-You-Should-Know.pdf

- **Tips for addressing emotional health:**
http://www.nationalmssociety.org/Living-Well-With-MS/Health-Wellness/Emotional-Health

- **Understanding and managing depression in MS:**
http://www.nationalmssociety.org/NationalMSSociety/media/MS-NationalFiles/Brochures/Depression-Multiple-Sclerosis.pdf

- **Driving and MS:**
http://www.nationalmssociety.org/NationalMSSociety/media/MS-NationalFiles/Brochures/Brochure-Driving-with-Multiple-Sclerosis.pdf

- **Understanding and managing cognitive problems in MS:**
http://www.nationalmssociety.org/NationalMSSociety/media/MS-NationalFiles/Brochures/Cognitive.pdf

- **Adherence to medications in MS:**
http://www.nationalmssociety.org/Treating-MS/Medications/Adherence

The **National Multiple Sclerosis Society** publishes many other resources (over 35 brochures and booklets) about various aspects of MS, including:

- Management of a variety of symptoms (not only cognitive and emotional, but also sleep problems, pain, gait/walking problems, urinary changes, spasticity, etc.);
- School-related issues (e.g., rights and responsibilities both for students and the schools, how to advocate for children/teens at the school, individualized educational plans);
- Work-related issues (e.g., when and how to disclose your condition at work, protections of the Americans with Disabilities Act, managing fatigue & cognitive issues on the job, telework options);
- Special considerations for children and teenagers (e.g., how to explain the condition, concerns and fears they might have);
- Review of medications used to treat MS (e.g., description, side effects).

These can be obtained by calling **1-800-344-4867** or they can be downloaded from their web site:
http://www.nationalmssociety.org/Resources-Support/Library-Education-Programs/Brochures

These same resources are also available in Spanish:

En español:
Aquí hallará información sobre diagnóstico y tratamientos, manejo de síntomas y asuntos laborales, así como información para cuidadores y niños. También hallará transmisiones educativas a través de la Internet, libros y enlaces a otros sitios educativos en la Internet. Para nuestras familias bilingües, cada título tiene su traducción en inglés y el enlace a su respectivo informativo (de así haberlo).

Si desea mayor información o para enterarse de los programas y servicios que se ofrecen, incluyendo nuestro programa nacional de educación por correo en español "Saber es Poder" (Knowledge is Power - KIP en inglés), por favor llame al 1-800-344-4867.

http://www.nationalmssociety.org/Resources-Support/Library-Education-Programs/Informacion-en-Espanol

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Student Corner

Volunteer & Leadership Opportunities for NAN Student Members

Victoria Merritt, M.S.
Graduate Student, Penn State University, NAN Volunteer Coordinator

Each year, the National Academy of Neuropsychology (NAN) recruits student volunteers to assist with the annual conference. In order to be eligible for volunteering, applicants must be an active Student Member of NAN and be able to commit to working 12-14 hours at the conference. Student membership is reserved for students who are enrolled in a full-time graduate program (i.e., pre-doctoral or graduate level students who are in the process of earning an advanced degree, including those on internship). Volunteer responsibilities are varied, and may include assisting with pre-conference preparation, conference registration, workshop monitoring and CE scanning, helping with the Student Raffle, as well as various other activities that make the conference run smoothly each year. In the past, selected volunteers have received many benefits, including free conference registration and free hotel accommodations (shared with other volunteers) during the time in which they volunteer.

Related to the abovementioned volunteer opportunity, NAN also recruits a student Volunteer Coordinator on an annual basis. This position requires attendance at the NAN Annual Conference for three consecutive years. During the first year, the successful applicant would serve as the Incoming Volunteer Coordinator, and would shadow and receive training from the current Volunteer Coordinators. Following this, the Incoming Volunteer Coordinator would transition into a two-year position as a Volunteer Coordinator. Similar to the requirements of a student volunteer, the Volunteer Coordinator must also be an active Student Member of NAN.

The main responsibilities of the Volunteer Coordinators are to work with the team of student volunteers and prepare a volunteer schedule for the annual conference. In doing so, specific duties include communicating with the student volunteers prior to the conference to identify availability, creating surveys, and assigning shifts to each student volunteer. In addition to arranging the volunteer schedules, the Volunteer Coordinators also work with NAN to coordinate hotel room assignments and workshop attendance for the student volunteers. While at the conference, the Volunteer Coordinators are in charge of ensuring that the student volunteers are adequately trained for their shifts. Additional conference responsibilities include general supervision of the volunteers, being on-call to assist with conference-related issues as they arise, and fielding questions or concerns from volunteers and conference attendees. Finally, another essential responsibility of the Volunteer Coordinators is serving as a student member of the NAN Program Committee. Involvement on this committee may include selecting presentations for the upcoming conference and assisting with conference programming preparation.

There are several benefits to being a Volunteer Coordinator. While serving in this capacity, there are many opportunities to present yourself as a leader—both to your fellow volunteers and to future colleagues. As a Volunteer Coordinator, you will also have the privilege of being able to meet and interact with prominent neuropsychologists in our field. Other benefits include free conference registration and free hotel accommodations for the duration of the conference. For more information, email nanstudentvolunteers@nanonline.org.

Students also have the opportunity to be involved in NAN by serving on other NAN Committees. NAN is comprised of a number of committees that contribute to the success of the entire organization, and several of these committees have student member representatives. Responsibilities of the student volunteers vary depending on the committee, and benefits include networking opportunities, developing leadership skills, and offering a unique contribution to NAN and the field of neuropsychology. Interested students can receive more information on the NAN website (nanonline.org).

Finally, the NAN Foundation has other opportunities for student volunteers who want experience in website and media. The positions require students who are familiar with camera usage and have great communication and collaboration skills. Additionally, NAN Foundation volunteers have opportunities to be involved in outreach projects. For additional information, contact the NAN Foundation.

Victoria Merritt is currently a doctoral student in Clinical Psychology at The Pennsylvania State University. She received her master's degree from Penn State in 2013, and is currently working on her dissertation research related to genetic factors and neuropsychological outcome following sports-related concussion. She has been a student member of NAN since 2012 and has served as a Volunteer Coordinator for NAN since 2013.

Things for Graduate Students to do at the NAN Conference

Jessica Meyer, M.S.
Graduate Student, Penn State University

Each year the annual NAN conference offers many opportunities for students including student-focused talks, social events, and the opportunity to work directly with NAN professional members. The 2014 NAN conference featured several student-focused talks and social events including a student luncheon with speakers focused on discussing work-life balance and the Women in Leadership networking event. Students presented their work along side NAN professional members in poster sessions, talks, and in case presentations.

The student-focused talks, free for all students and trainees, provided attendees with information on career opportunities outside of academia for which neuropsychologists are well qualified. A talk on alternative careers featured neuropsychologists working for a contract research organization, a test publishing company, the National Institutes of Health (NIH), and a pharmaceutical company. The panelists shared how they decided to pursue their respective careers and the steps they had to take to get there. They additionally provided candid advice about the pros and cons of their jobs and their typical workload. Another student-focused talk highlighted strategies used by the speaker in starting a successful private practice. Students additionally had the opportunity to attend an introduction to NIH grant writing session as well as talks focused on Parkinson's disease and the management of chronic pain.

The student lunch featured three panelists who discussed strategies for maximizing work-life balance and staying healthy. Each panelist shared their personal stories of how they have balanced their responsibilities at work and at home and shared the challenges they faced and how they overcame them. Advice from the panelists included: 1) setting priorities and goals both at work and at home; 2) deciding what is important to you and being kind to yourself about that decision; 3) making sure to prioritize your own mental and physical health; 4) and finding a mentor with whom you can comfortably discuss issues of work-life balance. The Women in Leadership event provided students with the opportunity to network with NAN professional members and to hear from featured speaker Dr. Estela S. Estape. Her talk, "In Pursuit of Your Dreams: Regardless of Age, Gender and Race," was engaging, funny, and stimulating for all.

Students' research was featured throughout the three poster sessions, and awards were granted for the best student research posters. Prior to the conference, six students were selected based on their poster abstracts to present their research in the student research presentations session. The Pediatric Grand Rounds featured several students presenting case studies, providing another opportunity for student involvement.

In addition to the informal networking opportunities provided throughout the conference, students had the opportunity to apply for the Women in Leadership Sponsorship Program. Through this program, seven students had the opportunity to be matched with leaders in the field of neuropsychology. Accepted students were able to shadow their sponsors throughout the conference, and had the opportunity to meet colleagues of their sponsors and foster new mentoring relationships.

The 2014 NAN conference provided students with an abundance of opportunities to showcase their own work and to network with professionals in the field, and featured programming focused on issues most relevant to trainees' needs. Each conference presents many of these same opportunities, and students are looking forward to the 2015 conference in Austin, Texas. I hope you will be able to attend!

Jessica Meyer is the study coordinator for the Sports Concussion Lab at the Pennsylvania State University, where she earned her MA in Clinical Psychology. Her work has focused on evaluating current methods of assessing the cognitive and emotional effects of sports concussion. For her thesis, she validated the use of a measure of affective bias for assessing verbal learning and memory in a sample of collegiate athletes at baseline and post-concussion.

Synopsis and review of: Sundgren, M., Maurex, L., Wahlin, A., Piehl, F., Brismar, T. (2013). Cognitive Impairment Has a Strong Relation to Nonsomatic Symptoms of Depression in Relapsing–Remitting Multiple Sclerosis, Archives of Clinical Neuropsychology 28 (2013) 144–155.

Review by Peter Arnett, Ph.D., Penn State University

Rationale for the study:
Cognitive problems are common in MS, with prevalence rates typically ranging from 45% to 65%, with variability often dictated by whether samples are community based or clinic based[1]. Many factors associated with MS may contribute to these difficulties. Disease related factors such as physical disability level, disease duration, brain atrophy, and white matter lesion load may predict cognitive difficulties, as well as factors liked fatigue, and depression. Depression is extremely common in MS, with lifetime prevalence rates typically around 50%[2]. Fatigue is also a common complaint in MS, with patients often reporting that it is their most debilitating problem. Prior research is mixed regarding the contribution of these variables to cognitive dysfunction in MS. Sundgren and colleagues'[3] study was designed to examine the relative contribution of all of these variables to cognitive dysfunction in MS.

An interesting feature of this study was the authors' examination of whether somatic or nonsomatic aspects of depression were most associated with cognitive dysfunction. This study element raises an important issue regarding depression in MS that has been frequently debated in the literature. In particular, because somatic depression symptoms (e.g., concentration difficulties, fatigue, sleep problems, sexual dysfunction) overlap with MS disease symptoms, how do we know whether they reflect depression or disease symptoms? By separating out such symptoms from nonsomatic depression symptoms (e.g., mood disturbance, negative evaluative thoughts), the authors allow for a fine-grained look at possible relationships with cognitive problems. Finally, given that many MS patients take psychotropic medication, the authors examined the possible positive or negative impact of medication on cognitive functioning in their sample.

Method:
A sample of 74 MS patients with Relapsing-Remitting MS (RRMS) was recruited from a hospital in Sweden. Eighty-nine healthy controls were also included. Cognitive outcome measures included the DKEFS subtests of Verbal Fluency, Color-Word Interference Test (CWIT), and Trailmaking Test (TMT); WAIS-III subtests of Digit Span, Digit-Symbol Coding, Block Design, and Symbol Search; and the Benton Visual Retention Test (BVRT-5), as well as a Vocabulary test. All cognitive scores were adjusted for age, sex, and education, and a global cognitive score was calculated that included all cognitive indices after they had been standardized.

As far as the authors' predictor variables, physical disability was measured by the Kurtzke Expanded Disability Status Scale (EDSS; Kurtzke, 1983)[4]. The Multiple Sclerosis Severity Score (MSSS) assessed disease severity. This measure combines indices of disease duration and physical disability. Depression was measured with the Beck Depression Inventory (BDI) and was further separated into a nonsomatic (items 1–13 – BDI-NS) and somatic scale (items 14–21 – BDI-S). Finally, fatigue was measured with the most commonly employed fatigue instrument in MS, the Fatigue Severity Scale (FSS).

Results:
Consistent with prior research, these investigators found significantly higher depression and fatigue scores in the MS group. Additionally, the MS group performed significantly worse on all neuropsychological tests except the visual memory measure. Thus, the sample is fairly typical of others reported on in the literature. The authors' Figure 1 (p. 149) provides an excellent summary of the relative correlations of all key predictor variables and the cognitive outcome measures. As shown, physical disability (EDSS score) was most consistently correlated with the cognitive measures, followed by the non-somatic depression scale (BDI-NS), and then fatigue (FSS). The somatic depression scale (BDI-S) was still correlated with most cognitive measures, but effect sizes were smaller. Surprisingly, the MS severity (MSSS) only correlated with one cognitive measure.

The authors further examined their data by including all of the variables that significantly correlated with cognitive outcomes in multiple regression analyses. Results showed that the non-somatic depression scale was the best predictor of cognitive outcomes, with effect sizes ranging from 12% (attention) and 22% (executive functioning) of variance accounted for, as shown in their Table 2 (p. 150). The core measure of physical disability (EDSS) was the next best predictor, accounting for between 8% (visual perception/organization) and 13% (both executive functions and processing speed). Fatigue also proved to be a significant predictor of cognitive indices, with effects ranging from 5% of the variance (visual perception/organization) to 10% (global cognitive

score). Not surprisingly, the combination of non-somatic depression symptoms and physical disability best predicted the cognitive outcomes.

Discussion:

Sundgren and colleagues' study underscores the importance of assessing depression, fatigue, and physical disability when trying to understand contributors to cognitive problems in patients with MS. Together, these variables explain up to nearly 25% of the variance in cognitive dysfunction in MS, with non-somatic depression symptoms being especially important. Thus, clinical practitioners would be well-advised to measure depression, fatigue, and physical disability systematically in neuropsychological evaluations of these patients. If these variables do indeed causally contribute to cognitive problems in MS, neuropsychologists should especially recommend aggressive treatment of both depression and fatigue in MS patients who show cognitive problems. Such treatment might thus result in improved cognitive functioning and, in turn, improved daily functioning and generally improved quality of life. As the authors rightly note, a significant proportion of MS patients with depression go untreated, so greater awareness of the need for treatment of this common outcome is needed. Fatigue can also be treated through both pharmacologic means and lifestyle changes.

One limitation of the authors' study is that they do not consider the possibility that the causal direction of some of these relationships could be reversed. For example, rather than depression causing cognitive problems in MS, the reverse may be true. Such an alternative model has been suggested by some work in my lab, where we found that cognitive problems predicted depression, especially in the context of maladaptive coping[5,6]. The correlational nature of studies from this literature make it difficult to draw confident causal conclusions. Still, data such as these do show that depression and cognitive problems in MS are often intertwined, and need to both be considered when formulating treatment plans.

Another limitation of this study is that the authors do not have a clear delineation of cognitive domains measured according to tests used. Specifically, a number of the tests they use are included in several cognitive domain calculations (e.g., the CWIT is used in the calculation of both the attention and executive domain composites). Although the authors correctly note that the tests they use are heterogeneous in relation to domains measured, it does make it difficult to draw conclusions about which cognitive domains are most clearly affected by depression in MS.

A final limitation of this study is that the authors did not adequately measure verbal memory. Only the Rey Auditory Verbal Learning Test was used, and this only in the case of 17 of the MS participants. Given that memory is often the cognitive domain most impacted by MS1, this is not a trivial oversight.

Despite its limitations, in the final analysis, Sundgren et al.'s study raises some important issues relevant to clinical practice in MS. Their study highlights the importance of attending to both somatic and non-somatic aspects of depression in MS, and also the fact that physical disability and fatigue levels should routinely be assessed systematically, so that their possible contribution to neurocognitive deficits in MS can be evaluated. The study further highlights the importance of recommending treatment for conditions like depression and fatigue in MS. Not only will such treatment lead to improved well-being and better quality of life, it also may positively impact cognitive functioning in these patients.

Dr. Peter Arnett received his Ph.D. in Psychology (Clinical) from the University of Wisconsin – Madison, and completed a post-doctoral fellowship in Clinical Neuropsychology at the Medical College of Wisconsin under the direction of Drs. Stephen Rao and Thomas Hammeke. He is currently a Psychology Professor and Director of Clinical Training at Penn State University. Dr. Arnett's research has focused on clinical neuropsychology, with an emphasis on studying secondary influences on cognitive functioning in persons with multiple sclerosis (MS) and mild traumatic brain injury. He is a fellow of the NAN, past winner of NAN's Nelson Butters Award for Research Contributions to Clinical Neuropsychology, was Program Co-Chair for the 2010 Mid-Year Meeting of the International Neuropsychological Society (INS), and is a board member of the INS. Dr. Arnett is the author of over 100 research articles and book chapters, and has edited a book entitled, *Secondary Influences on Neuropsychological Test Performance*. He is an editorial board member of several journals, and has received grant funding from the National MS Society, NIH, and NIMH.

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Professional Issues

Promoting healthy brain behaviors in Clinical Neuropsychology: An Examination of Medication Adherence in MS

Joanie Thelen, M.A. and Jared Bruce, Ph.D.
University of Missouri – Kansas City

Approximately 85% of patients with Multiple Sclerosis (MS) present for treatment with a relapsing-remitting disease course characterized by acute symptom exacerbations followed by periods of remission. Common symptoms include physical disability, pain, fatigue, cognitive difficulties, sensory disturbances, and depression. Treatment usually involves direct symptom management and brief corticosteroid therapy for acute exacerbations. Additionally, the National Multiple Sclerosis Disease Management Consensus Statement endorses initiating a disease modifying therapy (DMT) following a diagnosis of active RRMS.[1] Regular use of DMTs has been shown to slow disease progression, reduce exacerbation frequency, prevent the formation of new lesions, and reduce inpatient hospitalizations.[2,3] Specifically, randomized controlled trials show that DMTs contribute to a 35-83% reduction in new lesion activity, a 33-68% reduction in annualized relapse rates, and as much as a 50% reduction in disease progression.[4] While moderately efficacious, the effects of DMTs are solely preventative; they do not repair previous damage or alleviate current symptoms. As such, the benefits of DMTs are not directly observed by patients. In contrast, patients frequently observe the unpleasant side effects commonly associated with DMTs, such as injection site reactions, stomach upset, and flu-like symptoms.[5]

Adherence can be described as a patient's ability to correctly follow a prescribed treatment regimen. Types of nonadherence include declining to initiate a suggested treatment, missing prescribed doses, and premature treatment discontinuation. Approximately 50% of patients with chronic disease demonstrate poor adherence in developed countries.[6] Poor adherence is also common in MS. It is estimated that approximately 20% of MS patients decline to initiate DMT upon diagnosis and 30-50% of patients may discontinue their treatments prematurely.[7-10] Among patients who continue to use DMT, approximately 1 of every 5 patients misses more than 20% of her doses.[11] As a result of widespread nonadherence, countless MS patients will experience an increased incidence of exacerbations and new brain lesions.

As many as 50% of MS patients experience depression at some point during the course of their illness.[12,13] Depression appears to be a significant contributing factor to nonadherence in MS.[14] A study by Mohr and colleagues found that MS patients with depressive symptoms are over 4 times more likely to prematurely discontinue DMTs.[15] Moreover, successful treatment of depression with psychotherapy and/or medication leads to improved adherence levels.[15] Another study found that almost 63% of MS patients with a current mood or anxiety disorder missed more than 20% of their prescribed doses over eight weeks of electronic monitoring. Compared to patients with no mood or anxiety disorder, these patients were nearly five times as likely to be nonadherent to their DMT regimen.[16] In the same investigation, memory problems were also associated with poor adherence. Specifically, MS patients with poor adherence performed significantly worse than patients with adequate adherence on tests of prospective memory and delayed list recall.[16] These results were consistent with the finding that many patients report "forgetting" as a common reason for missing doses.[17]

Disease activity and exacerbation history are also significantly correlated with poor adherence in MS. Patients with a history of recent relapses demonstrate better DMT adherence than patients who have recently experienced a period of relative disease stability. Similarly, patients who have recently undergone steroid treatment for acute symptom relief are more adherent to DMTs than patients who have not received recent steroid treatment.[18] MS patients with relatively sparse disease activity often perceive no immediate benefit from DMTs, and in fact, may feel worse in the short term due to undesirable side effects.[19,20] These side effects can significantly reduce quality of life and likely deter DMT adherence among patients with inactive disease. Alternatively, patients with elevated disease activity may be more motivated to adhere to DMTs in order to prevent further disease progression. This pattern of DMT use is problematic. Immunomodulatory therapies are prescribed to prevent future exacerbations, and cannot undo past damage to the central nervous system.[21-23] The clinical utility of DMT is diminished among patients who choose to forgo medication when they are feeling well, only to re-initiate medication following acute symptom exacerbations.

Surprisingly, research suggests that most physicians are not aware that DMT adherence is a problem in MS. Using data from the global MS Choices Survey, Riñon and colleagues found that 59% of providers did not believe that adherence was a problem in MS.[24] As a consequence, providers may not assess patients' adherence or barriers to treatment. Improvements in patient-provider communication may be a key factor in increasing DMT adherence in patients with RRMS. Maintaining an open, non-judgmental clinical environment may help patients candidly discuss their medication and other treatment obstacles. Supporting this viewpoint, Berger and colleagues found that MS patients who received motivational interviewing (MI) counseling were significantly less likely to discontinue their DMT compared to patients receiving standard care.[25] Similarly, Turner and colleagues found that patients who received 3 MI counseling sessions missed

fewer doses of DMT than patients who received no counseling.[26] MI is a goal-oriented style of counseling designed to foster motivation for behavior change while simultaneously supporting patient autonomy.[27] In MI, counselors encourage patients to explore their ambivalence towards changing a specific behavior. Counselors are discouraged from persuasive or argumentative language, which may provoke resistance in the patient. Rather, the counselor promotes self-efficacy, encouraging patients to realize the possibility of meaningful health change.[28] Currently, our group is examining the efficacy of a Motivational Interviewing and Cognitive Behavioral therapy (MI-CBT) intervention to improve DMT re-initiation among RRMS patients who prematurely discontinue treatment. If proven efficacious, these counseling methods may represent one means by which neuropsychologists can increase behaviors that preserve and improve brain health among patients with MS.

Traditionally, clinical neuropsychologists have focused on the assessment and treatment of existing cognitive difficulties (e.g., differential diagnosis, treatment coordination, and cognitive rehabilitation). Conventional neuropsychological interventions rarely aim to preserve brain function among patients at risk for cognitive decline. In addition to promoting healthy lifestyles that are conducive to brain fitness (e.g., helmet use, exercise, healthy diet, abstinence from cigarettes), clinical neuropsychologists should develop and implement treatments that improve adherence to pharmacological interventions designed to prevent neurologic decline. As an integration of neuropsychology and traditional health psychology, health neuropsychology focuses on the promotion of brain health among individuals at risk for cognitive decline. By incorporating empirically supported treatments designed to improve adherence and promote healthy lifestyles in MS, clinical neuropsychologists would be at the forefront of an emerging body of literature emphasizing lifelong brain hygiene.

Clinical Take Home Points:

1. For patients with RRMS, successful use of disease modifying therapies (DMTs) can preserve brain health by slowing disease progression and reducing the number of exacerbations.
2. Between 30-50% of RRMS patients do not maintain proper adherence to DMTs.
3. Poor adherence in MS has been linked to mood disturbance, perceived treatment risks, and perceived disease severity.
4. Clinical neuropsychologists should develop interventions that increase adherence and other health behaviors to prevent neurologic and cognitive decline.

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Reserve Against Cognitive Impairment in Multiple Sclerosis

James F. Sumowski, Ph.D.

Cognitive Impairment in Multiple Sclerosis

More than half of persons with multiple sclerosis (MS) experience cognitive decline, especially slowed processing speed and memory problems.[1-3] Importantly, there is great variability in cognitive function across persons with MS, even among persons with similar disease burden.[2,3] How are some persons better able to withstand MS disease without cognitive impairment?

Brain Reserve against Cognitive Impairment

Paul Satz, Ph.D. developed the theory of brain reserve capacity[4] which proposed that cognitive impairment emerges when brain volume falls below a critical albeit unspecified threshold. This theory has been supported by observations that elders with larger head circumference or intracranial volume (proxies of the brain's maximal lifetime brain growth [MLBG]) are at reduced risk for cognitive decline or dementia (e.g.,[5]). Larger brain volume is linked to greater neuronal count,[6] which may underlie (a) more robust neural networks resistant to disease-related disruption and / or (b) more degrees of freedom for the brain to plastically reorganize in the face of aging or disease-related challenges. We have recently shown that larger MLBG protects against cognitive impairment in persons with MS. More specifically, larger MLBG (estimated with intracranial volume) moderated / attenuated (a) the deleterious link between MS disease burden (e.g., T2 lesion volume) and cognitive efficiency in a cross-sectional sample,[7] and (b) decline in cognitive efficiency over 4.5 years.[8] Note that MLBG was unrelated to memory function within our MS samples, and closer inspection of the aging literature suggests that MLBG is protective against cognitive inefficiency rather than memory deficits (see discussion[7]).

Although MLBG is almost completely heritable and therefore outside of one's current control, patients could be counseled regarding brain healthy choices which may prevent / delay the loss of reserve brain volume, such as smoking cessation, cardiovascular fitness, and maintaining a healthy diet to reduce risk factors for additional diseases (e.g., diabetes). This notion of maintaining brain reserve by avoiding risk factors / neuropathology is reviewed elsewhere as the concept of "brain maintenance" in aging.[9] Toward this end, patients with MS should be counseled against poor lifestyle choices associated with poor brain maintenance in general (e.g., obesity), as well as choices more specifically related to MS. For instance, we know that cigarette smoking[10] and psychological stress[11] are particularly damaging for MS patients, whereas disease modifying therapies are effective in reducing cerebral atrophy (preserving brain reserve).[12]

Cognitive Reserve against Cognitive Impairment

The cognitive reserve hypothesis[13] developed by Yaakov Stern, Ph.D. posits that enriching life experiences are linked to greater capacity and efficiency of neural networks, which then protect against cognitive decline in the face of aging and neurologic disease. Support for the cognitive reserve hypothesis has come from evidence that persons with greater educational or occupational attainment (e.g.,[14]) or engagement in cognitively stimulating leisure activities (e.g.,[15]) are at reduced risk for dementia. Indeed, greater intellectual enrichment attenuates the deleterious effect of AD neuropathology on cognitive status (e.g.,[16]). Research by myself and others has extended the cognitive reserve hypothesis to persons with MS (for review[17]), showing that MS patients with greater literacy / vocabulary (e.g.,[8,18]), education (e.g.,[19,20]), and engagement in leisure activity (e.g.,[7,21]) are protected against disease-related cognitive decline.

Cognitive reserve is an appealing concept, as it suggests that persons can reduce their risk of age- or disease-related cognitive decline by actively pursuing intellectually-stimulating lifestyles. It is important to emphasize, however, that evidence for the cognitive reserve hypothesis in aging and MS is almost entirely observational, thereby preventing causal statements about the protective effects of cognitive stimulation. There is some preliminary evidence that programs of cognitive training may increase reserve in aging;[22] however, a great deal more work is needed before we can "prescribe" specific programs of enrichment, including true experiments / randomized controlled trials of intellectual enrichment. That said, engagement in mentally-stimulating activities represents a cost-effective, non-invasive way for MS patients to actively participate in their own cognitive health. This is non-trivial, as the unpredictable nature of MS disease often results in an external locus of control,[23] leading to hopelessness and depression. MS patients should be encouraged to remain cognitively active from the time of diagnosis onward.

Reframing Brain Reserve and Cognitive Reserve

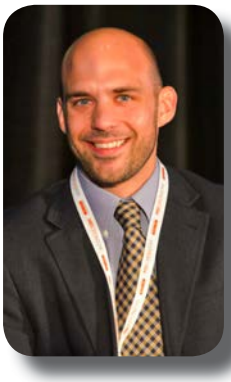
There is a tendency to isolate concepts of brain reserve and cognitive reserve, which I have done herein to remain consistent with the literature. Brain reserve is often discussed in terms of brain structure, and cognitive reserve is discussed in terms of brain network function. This is likely overly simplistic, because we must believe that brain structure is related to the functioning of networks, and recent evidence in aging[24] and MS[25] has linked cognitive leisure activity with larger hippocampal volume, indicating that our behavior impacts brain structure. These findings highlight hippocampal volume as part of the neuroanatomical basis of reserve (see discussion[25]), thereby encouraging us to investigate / develop interventions targeting hippocampal health and neurogenesis. One of the most promising cognitive treatments across neurologic populations may be aerobic exercise training. Basic animal research shows that aerobic exercise stimulates hippocampal neurogenesis and improves memory (e.g.,[26]), a finding which is being translated into humans (for review[27]). For instance, moderate intensity exercise training leads to increased hippocampal volume and memory in elders.[28] We have reported preliminary data extending these findings to MS,[29] and aerobic exercise training in progressive MS patients appears promising.[30]

Clinical Take Home Points:

1. Clinical consideration of intellectual enrichment and MLBG may assist in the early identification of MS patients at highest risk for future cognitive decline, which is important for the science and clinical practice of preventative medicine. These patients can then be targeted for early intervention and/or cognitive rehabilitation.

2. Persons with MS should be encouraged to engage in mentally-stimulating and physically-active lifestyles to help prevent cognitive decline.

3. Randomized controlled trials of intellectual enrichment are needed to provide causal evidence that reserve against cognitive decline can be enhanced.



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Multiple Sclerosis and Driving

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Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative disorder of the central nervous system that is associated with physical, cognitive, and psychological impairments that can negatively affect various aspects of independent functioning. One essential aspect of functional independence is the ability to drive a motor vehicle. The demands of driving have been examined in a variety of neurological populations - many of the identified relevant domains, such as cognition, physical and sensory factors have been found to be relevant to the current understanding of driving capacity among individuals with MS.

Driving behaviors among drivers with MS

When participants with MS are asked about their driving habits, they report a notable difference in driving behavior after being diagnosed.[1] For example, individuals with MS report they drive fewer days per week than matched healthy controls. This is particularly true for individuals with high scores (reflecting greater disability) on the Expanded Disability Status Scale (EDSS), a common measure used to evaluate the severity of MS, whereby increased EDSS was related to decreased driving frequency. Drivers with MS also reported decreasing risky driving behaviors after diagnosis, such as driving fast or drinking and driving. This limiting of unsafe behaviors seems to increase with severity of MS, as individuals with higher EDSS scores reported the most changes in unsafe driving. Taken together, the findings suggest that drivers with MS experience changes in driving behaviors but also demonstrate awareness and voluntary changes to driving.[1]

Similar findings have been reported by other groups, examining self-reported questionnaires. Specifically, survey results revealed that drivers with MS reported driving shorter maximum distances and shorter amounts of time than non-MS drivers. They also reported more fatigue than the control participants, and that this fatigue, along with other factors, affected their driving. Many of the MS participants also reported more changes in driving habits due to their symptoms and the fatigue, such as driving shorter distances, taking more breaks, and avoiding driving in bad weather or at night.[2]

Cognition

Research on MS and driving ability has suggested that the presence of cognitive and physical impairments can impact driving related skills. For example, studies have demonstrated that the presence of cognitive impairment alone can negatively affect performance on computerized measures of driving skills.3 Specifically, researchers compared performance of individuals with MS with and without cognitive impairment on two computerized driving measures: the Useful Field of Vision test (UFOV) and the Neurocognitive Driving Test (NDT). Participants with MS and cognitive impairment (MS+) performed worse on the NDT on measures of latency than MS participants without cognitive impairment (MS-) and healthy controls, suggesting that MS+ participants may have a deficit in processing speed that may be affecting their driving. Deficits were also detected on the UFOV, in which the MS+ group had a higher percentage of individuals categorized as a high risk for motor vehicle involvement.[3] Similar findings have been reported in a recent study, which found that individuals with MS performed significantly worse on the divided attention and selective attention subtests of the UFOV than the healthy controls.[4]

Similarly, in a follow up study examining Department of Motor Vehicles (DMV) records of the three groups, results indicated a higher frequency of documented accidents among drivers of MS with cognitive impairment when compared to healthy controls and MS drivers without cognitive impairment.[5] Interestingly, there was no difference in the number of driving violations observed between the three groups. More recently, Dehning et al[6] reported that drivers with MS had more driving violations than healthy controls for nonmoving safety violations and administrative violations (but not for speeding, alcohol, or moving safety violations). This study also utilized neuroimaging to examine structural differences, specifically the width of the third ventricle. The authors suggested that third ventricle width was a significant predictor of total driving violations.

Overall several studies have helped to define the contribution of cognitive functioning on driving performance among drivers with MS. Specifically, areas of attention, information processing speed, executive functioning, and visuo-spatial skills are relevant to driving performance in this clinical population.[3,5,7-8]

Physical Considerations

One notable test used to examine impairment is the Multiple Sclerosis Functional Composite (MSFC), which consists of three measures: upper and lower extremity functioning, and cognitive function. The MSFC was found to be correlated with the overall UFOV score, along with the visual-information processing and selective attention subsections.[9] The study also reported a correlation between MSFC and latency scores from the NDT, but not the error scores, indicating that drivers with MS were less efficient in responding to stimuli compared to drivers without MS. Notably, there was also a correlation between the MSFC and the number of crashes as reported in the DMV records. Individual examination of the three subtests of the MSFC indicated that cognitive function was significantly related to the driving performance indicators, including the UFOV overall score, the 3 UFOV subtests, and the NDT latency score. The hand and leg function subsections yielded fewer significant correlations, which may have been due to restricted range of physical symptoms in the sample. Similarly, using a driving simulator, researchers found that EDSS scores were not correlated with accident rates, but the MSFC score, specifically the PASAT subtest, was correlated with accident rates.[7]

Researchers examining the specific contributions of lower limb spasticity have reported that increased spasticity is associated with specific driving errors, including maintaining speed and following another vehicle.[10] Drivers with MS demonstrated significantly higher speed, increased speed variability, greater lane position variability, and slower response times. Spasticity was found to be associated with speed variability and following a lead car, while cognitive functioning was associated with lane position variability and response times during a divided attention task.

Vision

It is reported that 90% of individuals with MS will have illness-related vision impairment.[11] Vision is essential to safe driving. One study conducted a preliminary study on the relationship between measures of visual impairment and driving performance among individuals with MS.[12] Results indicated that deficits in color perception, but not in visual acuity or depth perception were related to driving performance in this study. Further work is underway to better define MS-related visual changes and driving.

Clinical Implications

Multiple sclerosis is a heterogeneous disorder, with variable symptom presentation, symptom duration and disease course. Driving is a highly regarded privilege that allows individuals to maintain a sense of autonomy and productivity; however, it may also be compromised by changes in cognitive, physical or sensory changes resulting from MS. While, ongoing research will continue to provide new insight into the relationship between MS impairments and driving capacity, existing studies can offer several helpful clinical considerations.

Clinical Take Home Points:

1. **Discuss issues or changes in driving capacity on a regular basis:** Too often driving is considered "outside" of the clinical realm and clinicians may fail to provide a forum for discussion about how changes in MS status may be related to driving ability.

2. **Do not underestimate the contributions of cognition:** Study results indicate that changes in cognitive ability, including attention, information processing speed, executive functioning, and visuo-spatial skills are relevant to driving performance in this clinical population.

3. **Adaptive driving equipment can minimize physical compromise:** Referrals for a comprehensive driving evaluation can help identify a variety of available adaptive equipment that can minimize the impact of upper and lower extremity deficits that may change throughout the course of MS.

4. **Vision is not just about acuity:** Given the variability in visual difficulties associated with MS, a comprehensive visual examination (including depth perception, contrast sensitivity, color perception, etc) should be included in determining driving capacity.

5. **Repeat, repeat, repeat:** Currently, MS is a life-long diagnosis, which is usually marked with variable symptom presentation. As such, evaluating driving capacity should not be a "one time" assessment. Given the changing and progressive presentation of MS, clinicians are encouraged to regularly discuss issues of driving capacity and to consider the benefits of repeated driving evaluations.

6. **Helpful Resources:**
   - Find a Certified Driver Rehab Specialist: www.aded.net
   - Physician's Guide to Assessing and Counseling Older Drivers: www.nhtsa.gov/people/injury/olddrive/olderdriversbook/pages/contents.html

Dr. Maria Teresa Schultheis is an Associate Professor with appointments in the Department of Psychology and the School of Biomedical Engineering, Science and Health Systems. At Drexel University, she serves as the Director of Clinical Training of the PhD program in Clinical psychology. Dr. Schultheis' clinical and research experience have been focused on the rehabilitation of cognitively impaired populations, including traumatic brain injury, stroke and multiple sclerosis. A main focus of her research is studying the demands of driving following neurological compromise which includes the development of new virtual reality driving assessment protocols. Dr. Schultheis' work was recognized early in her career in student awards from the National Academy of Neuropsychology and the Philadelphia Neuropsychological Society. She is also the recipient of the 2007 American Psychological Association Early Career Award for Division 40 (Clinical Neuropsychology).

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Physical Activity and Health-Related Quality of Life in Multiple Sclerosis

Robert W. Motl, Ph.D.

Multiple sclerosis (MS) has a prevalence of ~1 per 1,000 persons in the United States (1). This disease is characterized by intermittent and unpredictable episodes of focal inflammation (2) that result in the demyelination and transection of axons in the central nervous system (CNS; 3). There further are neurodegenerative processes presumably characterized by insufficient neurotrophic support within the CNS that occur later in MS (3). The pathophysiology of MS results in symptoms, neurological and functional impairment, and disability progression. The pathophysiology and its manifestations further compromise health-related quality of life (HRQOL) (4).

HRQOL: Definition and Status in MS

HRQOL represents a multidimensional term (5) often described based on physical and mental components of health status consistent with the Medical Outcomes Study, Short Form-36 (6). Those with MS have lower scores on components of HRQOL than non-diseased populations (4) and those with chronic diseases (7-9). Several features of MS likely explain compromised HRQOL, including (a) onset during the productive years of one's life, (b) uncertain and unstable disease course, (c) diffuse effects on mental and physical processes, and (d) absence of conclusive disease-modifying treatment (4). The improvement of HRQOL is an important goal of clinical research and care of persons with MS, and might be accomplished by identifying and targeting factors that influence this construct.

Factors Influencing HRQOL in MS

Many factors influence HRQOL in persons with MS, and factors that are modifiable represent targets of interventions for improving HRQOL. One literature review has identified possible modifiable factors including anxiety, depression, self-efficacy, pain, and fatigue as predictors of HRQOL in MS (4). Anxiety and depression were significantly and negatively correlated with HRQOL in a cross-sectional study of MS patients, even after controlling for disability status (10). Another study reported that personal beliefs regarding confidence in coping with challenging situations (i.e., self-efficacy) were positively associated with HRQOL (11). Pain was inversely correlated with aspects of HRQOL in a cross-sectional study of persons with MS (12). Fatigue has been negatively correlated with aspects of HRQOL in a cross-sectional study of MS patients (13). Interestingly, those factors are seemingly modifiable via participation in physical activity.

Physical Activity and HRQOL in MS

Physical activity is a lifestyle factor that has been associated with many benefits in MS. Physical activity is a behavior that involves bodily movement produced by contraction of skeletal muscles and results in increased energy expenditure compared with rest (14). Physical activity can be accumulated through leisure, occupational tasks, household chores, transportation, sport, and exercise. Some benefits of physical activity for persons with MS include increased strength and cardiorespiratory fitness, management of fatigue and depression, and improved walking mobility (15). Physical activity is associated with a slight reduction in the risk of MS relapse and has produced few adverse events (16).

Physical activity may have additional benefits for HRQOL. This is noteworthy, as an improvement in HRQOL through physical activity might be an even more meaningful outcome than general health benefits (17). One study examined the association between self-reported and objectively measured physical activity and HRQOL, using generic and disease-targeted instruments, in persons with MS (18). The results indicated that physical activity was positively associated with HRQOL, and this did not differ based on type of physical activity measure or HRQOL instrument. We recently reported that change in physical activity over a 12-month period was associated with changes in HRQOL in a sample of 269 persons with MS (19). Of note, multiple clinical trials have examined the effect of exercise training on indices of HRQOL in MS, and the overall effect has been summarized using meta-analysis (20). The cumulative evidence demonstrated that exercise training yielded a small improvement in HRQOL (g=0.23), and such improvement has been replicated in interventions of lifestyle physical activity (21).

Physical Activity and HRQOL: Self-efficacy as a Mediator?

The association between physical activity and HRQOL probably is indirect and accounted for by factors such as self-efficacy. This was initially based on conceptual arguments by Stewart and King (5) who conceptualized a comprehensive framework of QOL outcomes for physical activity research with older adults. This framework considers physical and mental health status as two broad HRQOL categories with several underlying elements that can be influenced by physical activity. The underlying elements of such a model are specific, proximal outcomes of physical activity and may be viewed as intermediate factors in a broader model that includes distal HRQOL outcomes (5).

That proposition was empirically established in research examining self-efficacy as a mediator of the association between physical activity and HRQOL among older adults (22). The study examined the associations among physical activity, self-efficacy, and HRQOL in older Black and White women as part of the baseline assessment of a 24-month prospective study (22). The analyses indicated that physical activity was indirectly associated with HRQOL through a pathway that included self-efficacy. That pattern of associations was later replicated with longitudinal data involving changes in physical activity, self-efficacy, and HRQOL over a 24-month period of time among older adults (23).

We are further aware of research that has focused on self-efficacy as a mediator of the association between physical activity and HRQOL in MS. One study tested the hypothesis that physical activity would be indirectly associated with HRQOL through a pathway that included self-efficacy (24). Participants were 133 persons with a definite diagnosis of MS who completed measures

of physical activity, self-efficacy, and HRQOL. Path analysis indicated that those with MS who were more physically active had greater self-efficacy for function and control, and self-efficacy for function and control were associated with greater HRQOL. Such associations have been replicated in a longitudinal investigation of naturally occurring changes in physical activity, self-efficacy, and HRQOL over 12 months in 269 persons with MS (19).

Summary

MS is associated with a substantial reduction in HRQOL. Physical activity is a modifiable lifestyle factor that is favorably associated with HRQOL in those with MS. This is noteworthy as physical activity is an inexpensive option for improving HRQOL with potential economic and personal payoffs for those with MS (17). To that end, researchers have made great strides in designing and testing behavioral interventions for increasing physical activity (25) and improving HRQOL, and clinicians can now focusing on promoting physical activity for improving the HRQOL of persons living with MS.

Clinical Take Home Points:

1. MS is associated with a reduction in HRQOL.
2. Anxiety, depression, self-efficacy, pain, and fatigue are consistent predictors of HRQOL in those with MS.
3. Physical activity is a modifiable lifestyle factor that is favorably associated with HRQOL in MS.
4. The association between physical activity and HRQOL is indirect and accounted for by intermediate factors such as self-efficacy.

Prof. Robert Motl has systematically developed a research agenda over the past decade that focuses on physical activity and its measurement, predictors, and consequences in persons with neurological diseases, particularly multiple sclerosis (MS). For example, Prof. Motl has generated a body of research on the validity of common physical activity measures in persons with MS. This has resulted in foundational research on quantifying differences in physical activity, particularly rates of moderate-to-vigorous physical activity, in MS vs. non-diseased controls. These two lines of research have provided the basis for examining the outcomes of physical activity in MS, resulting in prominent papers on beneficial changes in cognition, depression, fatigue, walking disability, and quality of life. Prof. Motl has undertaken research on social-cognitive predictors of physical activity that has informed the design and delivery of behavioral interventions for increasing physical activity in MS. This research has been continuously funded by the National MS Society and National Institutes of Health since 2003.

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New Research on Cognitive Fatigue in Multiple Sclerosis

Joshua Sandry, Ph.D., Ekaterina Dobryakova, Ph.D., and John DeLuca, Ph.D.

Multiple sclerosis (MS) is a disabling neurological disorder with pathology that involves lesions, plaques and axonal demylenation across the central nervous system. The clinical expression of the disease is extremely heterogeneous across patients, with impaired sensory, motor, emotional and cognitive function. Fatigue may be one of the most common symptoms that MS patients experience and prevalence estimates of fatigue range between 70% and 90%[1]. Operationally defining cognitive fatigue (CF) has proven to be challenging; however, from a patients' perspective, CF might be best characterized as the feeling of being "mentally drained". The experience of CF can result in subjective sensations or objective performance changes, recently referred to as fatigue and fatigability, respectively[2]. Over the past few years, research in our lab has focused on understanding the behavioral parameters that bring about feelings of CF, as well as the neural correlates of CF in MS. Identifying the underlying causes of CF and isolating the neural networks involved in CF will lead to more efficient clinical techniques that can be used to manage CF in MS. In this brief article we highlight some of our recent work in this area and provide a few take home practice points for clinicians.

Cognitive Fatigue and Behavior

CF is multifaceted and the measurement of the construct is complex[3]. Questionnaires exist that are designed to capture general fatigue; however, many scales lack items that specifically capture CF. The scales that do include CF items often ask patients to retrospectively estimate their fatigue over the past week or few weeks. A large proportion of prior research has focused on using these "trait" measures to understand CF in MS. We have taken a different approach and that is to look at "state" CF and try and identify what task demands elicit subjective feelings of CF. Taking online measurements of CF (i.e., state CF), asking participants how mentally fatigued they are at this very moment, has been valuable in trying to understand how different task demands lead to subjective feelings of CF in MS.

In our earlier work, we recorded subjective trait CF ratings at four separate intervals over a 3-hour neuropsychological testing session and found that CF ratings were unrelated to behavioral performance. In fact, MS participants' neuropsychological performance improved similar to healthy controls (a practice effect), suggesting that higher fatigue does not impair performance[4]. Cognitively impaired and unimpaired MS patients also show similar CF profiles[5] and high and low fatigue periods in the same MS patients do not differ in their cognitive performance[6]. These findings suggest that subjective CF does not change as a function of cognitive impairment and that individual differences in CF do not impact cognitive performance. More importantly, this work shows that subjective CF does not correlate with objective performance, a consistent finding with over 100 years of research.

In order to further identify the task parameters associated with CF, we recently asked MS participants to complete two cognitive tasks that varied in task difficulty[7]. One task relied on working memory resources (n-back) while the other task relied on processing speed resources (modified symbol digit modalities test) and each task included either a low or high cognitive demand. Participants' "online" or state CF was measured at multiple specific intervals allowing us to identify how CF manifests as a function of: [1] cognitive domain (working memory vs processing speed) [2] cognitive load (high vs low) or [3] time on task, as well as the interaction among these factors. The findings revealed that subjective CF was more pronounced as the length of the task increased and this was more extreme for MS patients compared to healthy controls. There was no effect for cognitive domain or cognitive load. Additionally, we found that trait and state measures of fatigue were uncorrelated in MS patients, suggesting that the two constructs are independent. Finally, consistent with prior research[3], higher levels of CF did not result in worse behavioral performance, supporting the fatigue-behavior dissociation. At this point, future research needs to test whether minimizing time on task (or taking more breaks) reduces CF and whether this will have important implications for clinical practice.

Neural Correlates of Cognitive Fatigue

Recent advances in functional neuroimaging have helped to understand the neurocognitive and neurobiological basis of CF. Neuroimaging evidence is particularly valuable since self-report instruments (e.g. Fatigue Severity Scale or modified Fatigue Impact Scale) that are often used to assess CF show little correlation with objective measures of performance as described above.

According to one hypothesis, CF might arise due to the "failure of the *non-motor* functions of the basal ganglia"([8]p.40). The basal ganglia is an aggregation of subcortical nuclei, previously thought to be responsible primarily for motor function and control[9]. However, today there is ample evidence that shows that the basal ganglia plays an important role in learning, motivation, addiction and reward-guided behavior. Largely, the involvement of the basal ganglia in higher-order behaviors can be explained by widespread topographical projections from the prefrontal cortex (PFC)[10]. The hypothesis proposed by Chaudhuri and Behan[8] was developed based on evidence from animal and clinical studies that showed the effects of the basal ganglia damage to be similar to the symptoms of patients who experience CF.

Functional neuroimaging studies can provide important converging evidence regarding the activity of brain areas underlying fatigue. To date, there are very few functional neuroimaging studies that investigate the neural correlates of CF in either healthy participants or in individuals with neurological damage. For example, functional magnetic resonance imaging (fMRI) studies from our lab showed that the pattern of activation in the striatum, the primary input nucleus of the basal ganglia, is different in individuals with MS and traumatic brain injury (TBI; prevalence estimates of fatigue up to 80%) compared to healthy participants[11,12]. Specifically, in both studies, we observed

a steady decrease in striatal activation across repeated blocks of a processing speed task in healthy participants. This is consistent with evidence from other neuroimaging studies that show healthy adults relying on striatal mechanisms early during task performance. In contrast, both MS and TBI participants showed increased or stable striatal activity across the task blocks, with a significant increase in PFC activation. This pattern of brain activity was observed despite no group differences in performance accuracy between healthy participants and MS/TBI participants. Further, this increase in striatal activation correlated with subjective CF[13].

Taken together, these data suggest that individuals with CF might have to recruit greater neural resources in order to maintain performance comparable to healthy individuals. Engagement of additional neural resources might result in increased effort leading one to feel CF. Indeed, it has been suggested that CF might be due to an effort-reward imbalance, i.e. an imbalance between the perceived amount of effort required by an action and the amount of reward that results from the action. That is, CF might result from inappropriate effort output and the perception that the outcome is not worth the effort[14]. In support of this hypothesis, neurophysiological studies with laboratory animals show that striatal lesions remove animals' preference to work for a larger food reward[15]. Such goal-directed behavior (exerting effort to obtain a reward) has been shown to depend on the neurotransmitter dopamine, suggesting a link between fatigue and dopamine levels in the brain. Several clinical trials showed the effectiveness of dopamine medication in reducing CF in various clinical populations, such as TBI, Parkinson's disease and chronic fatigue syndrome.

The influence of dopamine on fatigue and associated brain activity in individuals with MS has not been investigated, either from pharmacological or from non-pharmacological perspectives. Our lab is currently conducting a clinical trial to see the effectiveness of dopaminergic medication on CF in MS. In addition, we are also investigating whether CF can be reduced through a non-pharmacological method (i.e. by means of reward presentation, a manipulation that has been shown to result in striatal dopamine release and changes in striatal activation). Preliminary evidence indeed shows that in both MS and healthy control participants, fatigue decreases when participants have an opportunity to obtain a reward[16].

Take Home Practice Points:

1. Subjective cognitive fatigue does not correlate with objective performance.
2. Time on task may affect subjective fatigue but not objective performance.
3. Subjective "state" cognitive fatigue does not correlate with traditional neuropsychological measures of "trait" fatigue.
4. Reward may reduce subjective cognitive fatigue, but additional research is necessary.
5. Dopamine imbalance might cause fatigue in clinical populations; more cross-discipline research is needed.

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Donald Stuss, PhD
"A different approach to the development of the concepts of the four categories of frontal lobe functioning, starting from clinical lessons – why clinicians have to be wary about what they see when assessing patients with frontal lobe dysfunction"

Closing Keynote:

Kenneth Heilman, MD
"Creativity and the Brain"