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Retrospective Analysis of a Comprehensive Concussion Recovery Program

Majid Fotuhi
NeuroGrow Brain Fitness Center & Johns Hopkins Medicine

Pritty Dwivedy
NeuroGrow Brain Fitness Center

Lauren H. Yeom
NeuroGrow Brain Fitness Center

Ifrah Nadeem
NeuroGrow Brain Fitness Center

Ali Y. Ebadi
NeuroGrow Brain Fitness Center

Maddison Miles
NeuroGrow Brain Fitness Center

Rachel K. Tittle
NeuroGrow Brain Fitness Center

Up to 25% of patients with mild traumatic brain injury develop post-concussion syndrome (PCS) and have persistent symptoms that last for months to years. In this retrospective analysis, we evaluated the NeuroGrow Concussion Recovery Program, a multi-disciplinary 12-week brain rehabilitation program that includes EEG-based neurofeedback and brain coaching (consisting of targeted cognitive stimulation and training for improved diet, exercise, sleep, and meditation). We compared the results of neurocognitive testing before and after treatment in 46 patients with PCS. After treatment, patients experienced significant improvement in most tested domains, with medium or large effect sizes. The average change in the "CNS Vital Signs" (CNSVS.com) Neurocognition Index was a score improvement of 10.56 points ($p<0.0001$, $dz=0.641$). Over 60% of patients who began in the "abnormal range" for Complex Attention, Cognitive Flexibility, and Executive Functioning experienced reliable, clinically significant improvement. The findings of this pilot study suggest that rehabilitation counselors can consider offering a combination of neurofeedback and brain coaching for patients with PCS.

Keywords: post-concussion syndrome, brain rehabilitation, neurofeedback

Traumatic brain injury (TBI) is defined as alterations in brain function caused by external physical force or rapid acceleration/deceleration (such as whiplash) (Arciniegas, Anderson, Topkoff, & McAllister, 2005; Menon et al., 2010; Pevzner, Izadi, Lee, Shahlaie, & Gurkoff, 2016). TBI can be classified as mild, moderate, or severe based on the initial score of the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974; Teasdale et al., 2014), the duration of loss of consciousness (LOC) at the time of injury (Forde, Karri, Young, & Ogilvy, 2014; McKee & Daneshvar, 2015), and the duration of post-traumatic amnesia (PTA). Patients with severe TBI have an initial GCS score of 3-8, experience LOC for more than 24 hours, and have PTA for more than seven days (McKee & Daneshvar, 2015). Patients with moderate TBI have an initial GCS score of 9-12, experience LOC for 30 minutes to 24 hours, and have PTA for 1-7 days. Patients with repeated

Majid Fotuhi, M.D., Ph.D., NeuroGrow Brain Fitness Center, 8280 Greensboro Drive, Suite 240, McLean, VA 22102.

Email: mfotuhi@neurogrow.com

TBIs are at increased risk of developing cumulative brain injury, and patients with a single remote moderate or severe TBI are at risk for developing motor dysfunction and parkinsonism later in life (Gardner et al., 2017; McKee & Daneshvar, 2015).

According to the American Congress of Rehabilitation Medicine (ACRM), patients with mild TBI (mTBI) have an initial GCS score of 13-15, experience LOC for less than 30 minutes, and have PTA of up to 24 hours (Kay et al., 1993). Most patients with mTBI feel better within 2-3 weeks and achieve full recovery within 90 days (Eme, 2017). However, some patients with mTBI, especially those who have a brain lesion caused by the injury (classified as complicated mTBI), can have disabling symptoms for months to years following the injury event. Although estimates differ, up to about 25% of patients with one or repeated mTBIs suffer from persistent symptoms that last longer than three months, a condition known as post-concussion syndrome (PCS) (Hiploylee et al., 2017; Polinder et al., 2018). These symptoms can include a combination of neurological, emotional, and sleep issues such as dizziness, vertigo, motion sensitivity, fatigue, headache, difficulty with reading and comprehension, irritability, anxiety, depression, memory loss, insomnia, noise/light sensitivity, mood swings, personality changes, and/or profound impairments in attention, processing speed, and executive function (Arciniegas et al., 2005; Eme, 2017; Reddy, Rajeswaran, Devi, & Kandavel, 2017). Thus, the labelling of "mild" in mTBI is misleading, as many patients experience dire consequences from their injury (Yamamoto, Levin, & Prough, 2018).

In addition to having persistent symptoms, patients with PCS – whether triggered by mTBI or moderate to severe TBI – experience a poor quality of life (QOL) and negative psycho-social effects, such as the breakdown of personal relationships, feeling disconnected from society, loss of employment, and experiencing threats to status and career opportunities (Reddy et al., 2017; Snell, Macleod, & Anderson, 2016). There is a pressing need to develop comprehensive rehabilitation strategies to help millions of patients with PCS achieve resolution of their symptoms and return to their baseline level of brain function (Corps, Roth, & McGavern, 2015).

Biofeedback and Other Rehabilitation Treatment Options for Patients with PCS

Biofeedback therapy has shown promising results in a wide range of neurological conditions, including stroke (Kondo et al., 2019). Biofeedback techniques that utilize operant conditioning have also been shown to improve voluntary muscle control after spinal cord injury (Brucker & Bulaeva, 1996). Along similar lines, a form of biofeedback called electroencephalogram-based neurofeedback (EEG-NFB) seeks to restore brain oscillations that are disrupted in conditions such as ADHD, epilepsy, and autism (Niv, 2013). In EEG-NFB protocols that utilize the z-score method, operant conditioning is used to reward the patient for modifying their brain activity toward the pattern in an age-matched normative database (Thatcher & Lubar, 2009). Given the benefits reported in other neurological conditions (Pineda, Carrasco, Datko, Pillen, & Schalles, 2014; Tan et al., 2009; Van Doren et al., 2019), EEG-NFB techniques have also been used for brain rehabilitation in patients with concussion and PCS (Duff, 2004; Munivenkatappa, Rajeswaran, Indira Devi, Bennet, & Upadhyay, 2014; Reddy, Rajeswaran, Bhagavatula, & Kandavel, 2014; Surmeli et al., 2017; Thompson, Thompson, Reid-Chung, & Thompson, 2013; Tinius & Tinius, 2000; Walker, Norman, & Weber, 2002; Zorcec, Demerdzieva, & Pop-Jordanova, 2011).

Many other therapeutic interventions have shown promising results for treating patients with PCS, either alone or in combination. These include education programs that teach patients about their disorder and how to cope with their symptoms (Ponsford et al., 2002), exercise therapy (Leddy et al., 2010), and pharmaceutical interventions for individual symptoms of PCS (e.g., using sleeping medications for treating concussion-induced insomnia) (Arciniegas et al., 2005). Recovery from brain injury in PCS might also be improved by activating natural repair mechanisms in the brain, including increasing levels of brain-derived neurotrophic factor (BDNF) and reducing inflammation (Corps et al., 2015; Francis & Stevenson, 2018; Wurzelmann, Romeika, & Sun, 2017), through a combination of diet, exercise (Estrada & Contreras, 2019; Griesbach, Hovda, & Gomez-Pinilla, 2009; Oliver, Anzalone, & Turner, 2018), and use of omega-3 fatty acid supplements (Bailes & Patel, 2014; Pu et al., 2017). These interventions have been shown to improve cognitive function and brain biology in cognitive decline with aging, which shares many characteristics with PCS (Blennow, Hardy, & Zetterberg, 2012; Fotuhi, Hachinski, & Whitehouse, 2009; Valls-Pedret et al., 2015). Thus, this combination can potentially provide disease-modifying treatment options for PCS patients, especially those who prefer to avoid taking pharmaceutical medications. Finally, rehabilitation counseling that guides patients to regain their confidence to function independently through engagement in recreational and leisure activities (RLAs) such as enjoyable hobbies, games, and social interactions can provide marked benefits toward their personal well-being and occupational success (Thomas, Burker, & Kazukauskas, 2015).

NeuroGrow Concussion Recovery Program

Although several therapeutic approaches have been used to treat PCS symptoms, there is currently no consensus in the field on a single effective treatment protocol for all patients with this condition (Blennow et al., 2012; Hadanny & Efrati, 2016). One likely reason for the lack of a widely accepted protocol is that patients with PCS suffer from a multifactorial set of symptoms (Snell et al., 2016) and thus no single intervention may work well for all patients. Therefore, a multi-disciplinary therapeutic approach that is tailored to each patient's specific set of symptoms may represent a more effective strategy for PCS.

Based on the literature summarized above, we developed a multi-disciplinary, comprehensive, and personalized "NeuroGrow Concussion Recovery Program" (NeuroGrow CRP; outlined in Figure 1). Briefly, after a thorough medical and neurological examination, patients undergo quantitative EEG (qEEG) and neurocognitive testing to establish the nature and relative severity of their cognitive and neuro-behavioral deficits. These results, along with each patient's medical history, are used to design their individualized NeuroGrow CRP. During their 3-month brain rehabilitation program, patients receive a combination of EEG-NFB (45 minutes) and Brain Coaching (45 minutes), twice a week. In one-on-one visits with their "brain coach" (who serves as a brain training coach and a life coach), patients are encouraged and trained to

improve their diet, exercise, sleep, time management, and stress management. They also engage in either computer-based brain training program (such as HappyNeuron.com) or hands-on brain games such as chess. Pharmacological treatment is provided, if necessary, for symptoms related to PCS such as depression, insomnia, anxiety, and migraine. When indicated, patients with vertigo are referred to professionals outside the clinic for vestibular physical therapy exercises. Patients undergo mid-program and post-program re-evaluation, with qEEG and neurocognitive testing, to monitor their progress and to make changes in their brain training protocols (if needed).

The purpose of this study is to perform a retrospective analysis of data collected from PCS patients who completed the NeuroGrow CRP, to evaluate and quantify any objective changes in their neurocognitive function after treatment.

Method

Participants

An IRB Privacy Board Waiver of Authorization for retrospective analysis of data (with all personal identifiers removed) was obtained from the New England Institutional Review Board. This study is a pre-post analysis of de-identified patient data from NeuroGrow Brain Fitness Center, a neurology practice in Virginia, USA. TBI patients who present to this sub-specialty neurology practice have already seen several health care professionals for evaluation and treatment of their persistent concussion symptoms and always have a prior diagnosis of concussion or TBI by other physicians. The criteria used for diagnosis with PCS includes a history of one or more TBIs with persistent symptoms that last more than 90 days beyond the relevant brain injury. NeuroGrow patients are eligible to enroll in the CRP if they are 8 years or older, have a diagnosis of PCS, have multiple objective deficits that adversely affect their lives, and do not have a concurrent diagnosis of dementia. PCS patients with few mild to moderate symptoms that are controlled through neurology outpatient visits (such as post-concussion headache that is responsive to medication) are not offered the opportunity to enroll in the program. Inclusion criteria for this retrospective study were: all children and adult patients with a diagnosis of PCS who started and completed the NeuroGrow CRP between 11-1-2016 and 12-31-2017. There were no exclusion criteria. Forty-six patients met these criteria and were included in the study. Demographics information and information about the TBI event that preceded patients' PCS symptoms is shown in table 1.

Table 1

Demographics

	number	%	*M*	*SD*
Male	16	35		
Female	30	65		
age in years			31.7	15.9
10 – 17	11	23.9		
18 – 30	15	32.6		
31 – 45	10	21.7		
46 – 60	7	15.2		
over 60	3	6.5		
months between patient's relevant TBI event[a] and start date of NeuroGrow CRP			22	43
3 – 6	13	28.3		
6 – 12	9	19.6		
12 – 36	18	39.1		
more than 36	6	13.0		
relevant TBI event was classified as:				
mild TBI (concussion)	46	100.0		
moderate TBI	0	0		
severe TBI	0	0		
relevant TBI event involved loss of consciousness				
Yes	15	32.6		
No	31	67.4		
number of previous concussions/TBIs experienced (prior to relevant TBI event)				
0	30	65.2		
1	9	19.6		
2	6	13.0		
3	0	0		
4	1	2.2		

Note. [a]relevant TBI event = the injury that directly preceded the patient's current PCS symptoms

Concussion Recovery Program Protocol

The NeuroGrow CRP protocol is described in a flow chart (Figure 1). During the initial appointment with the neurologist, patients undergo a thorough medical and neurological examination, including review of their medical history and medications. All patients with PCS also undergo neurocognitive evaluation and qEEG. If indicated, patients are referred for tests to assist with their full baseline evaluation. These may include MRI, sleep study, vestibular testing, or cardiopulmonary exercise test.

The NeuroCognitive Evaluation step in the protocol consists of a series of objective cognitive tests as well as three questionnaires about concussion-related symptoms:

- CNS Vital Signs (CNS VS) (Gualtieri & Johnson, 2006) is a battery of computer-based cognitive tests that compare the patient's results with age-matched normative controls. The cognitive domains utilized include: neurocognition index, composite memory, verbal memory, visual memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, executive functioning, working memory, sustained attention, simple attention, and motor speed.
- NeuroGrow's in-house "Brain Fitness Calculator" is a questionnaire (with 15 questions) that checks for factors that are associated with optimal brain health. These include level of daily exercise, adherence to a healthy diet, usage of omega-3 supplements, quality of sleep, social engagement, extra-curricular activities/hobbies, positive attitude, and mood (Supplemental Figure 1). Some questions address QOL such as their "love of daily routine," and "peaceful state of mind."

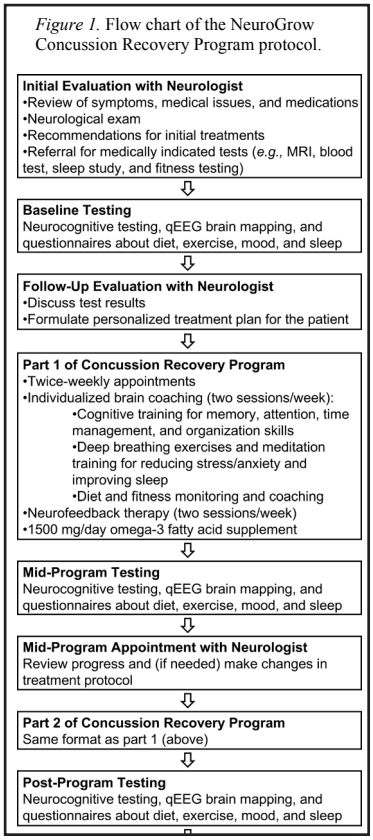


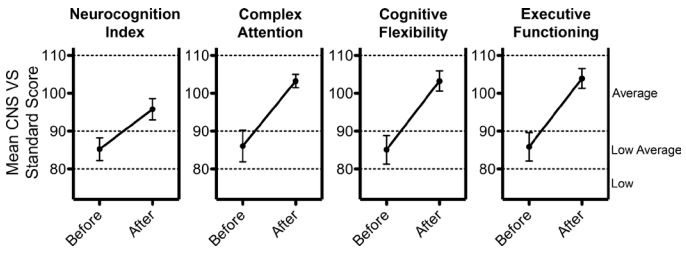
Figure 1. Flow chart of the NeuroGrow Concussion Recovery Program protocol.

- NeuroGrow's in-house "Concussion Symptoms Questionnaire" is a checklist of 15 neurocognitive and 20 neurobehavioral symptoms that can occur in patients with PCS (Supplemental Figure 2). These include questions about memory loss, attention issues, headaches, sensitivity to light/sound, irritability, and sad mood.
- Epworth Sleepiness Scale (ESS) (Johns, 1991, 1992; Johns & Hocking, 1997) is a commonly used questionnaire that addresses patients' level of daytime sleepiness.

Quantitative EEG brain-mapping is performed by trained technicians using the Discovery software from BrainMaster Technologies (www.BrainMaster.com) and by the TruScan from Deymed Diagnostic (Deymed.com). EEG data are further analyzed with software and normative databases from NeuroGuide (http://www.appliedneuroscience.com).

Figure 2. Scores for CNS VS domains most relevant to concussion improve after treatment.

Mean CNS VS domain scores before and after NeuroGrow CRP treatment; error bars indicate *SEM*. The mean increase in score after treatment is statistically significant for all four domains.



Brain Fitness Calculator

People's day-to-day lifestyle choices and activities have a profound impact on their brain health and function, both in the short term and long term. The Brain Fitness Calculator is a series of questions about modifiable factors in a person's life that can give us hints on how well they are taking care of their brains at this time and what will be the trajectory for their brain function - and size - in the future. The score from this assessment can provide incentives for people to become proactive toward building a stronger brain and appreciate how simple tweaks in their daily activities can reshape their brain for decades to come.

Green (Good job, keep it up): 60-75 Orange (Need some work): 45-59 Red (Need lots of work): 15-44

	Your Score
Energy level throughout the day (low: very tired to high: very energetic)	1 2 3 4 5
Fitness (low: totally out of shape to high: in great shape)	1 2 3 4 5
Peaceful state of mind (low: stressed out and nervous to high: calm and in control)	1 2 3 4 5
Organized (low: chaos at home and work to high: well-organized most of the time)	1 2 3 4 5
Positive attitude (low: life is tough; everything will fail to high: life is beautiful; everything will work out just fine)	1 2 3 4 5
Satisfactory sleep (low: trouble falling sleep or up all night to high: sleep well, about 8 hours a night)	1 2 3 4 5
Memory for names (low: can't remember anybody's name to high: remember everybody's name)	1 2 3 4 5
Taking Brain Vitamins (low: never or one day a week to high: 5 or more days a week)	1 2 3 4 5
Social engagement (low: prefer to stay alone by myself to high: busy with lots of social activities every week)	1 2 3 4 5
Sense of curiosity (low: not too much into figuring things out to high: love to discover new things and solve puzzles)	1 2 3 4 5
Love your daily routine (low: dread my day-to-day routine to high: enjoy and love my daily routine)	1 2 3 4 5
Heart healthy diet choices (low: fast food, donuts, French-fries to high: lots of fruits and vegetables, zero junk food)	1 2 3 4 5
Mindful of portion size (low: eat large portions and second servings to high: prefer small and reasonable portions)	1 2 3 4 5
Extracurricular activities / hobbies (low: do not enjoy participating in activities to high: enjoy trying new hobbies, participating in community activities, volunteering, or helping others in my community)	1 2 3 4 5
Usual mood (low: down and depressed to high: happy and cheerful)	1 2 3 4 5
Add up your score:	

Supplemental Figure 1. NeuroGrow's Brain Fitness Calculator. All entry ratings (1 to 5) are summed to yield the total score.

During the follow-up appointment with the neurologist, the results of tests and questionnaires are discussed in detail. Patients who meet the criteria for enrollment in the NeuroGrow CRP (described previously) receive information about the details of this program and are offered the option to enroll. When necessary, medications are prescribed for symptoms related to PCS such as depression, insomnia, anxiety, and/or migraine. Patients also receive referral for vestibular therapy if they have objective evidence of any vertigo, gait imbalance, or disequilibrium.

Concussion Symptom Questionnaire

The general symptom questionnaire is a series of questions about your symptoms on a day to day basis. The score from this assessment can provide information that our team can use to assist you in feeling sharper, calmer, and happier.

Please rate the following symptoms on a scale of 1 to 10 (1 being mild symptoms; 10 being severe symptoms).

Neuro-cognitive Symptoms and Issues	Your Score Mild symptoms .... Severe
Difficulty Paying attention	1 2 3 4 5 6 7 8 9 10
Difficulty with calculating	1 2 3 4 5 6 7 8 9 10
Difficulty with concentrating	1 2 3 4 5 6 7 8 9 10
Difficulty with making decisions	1 2 3 4 5 6 7 8 9 10
Difficulty with multitasking	1 2 3 4 5 6 7 8 9 10
Difficulty with navigation	1 2 3 4 5 6 7 8 9 10
Difficulty with processing information quickly	1 2 3 4 5 6 7 8 9 10
Difficulty with understanding instructions	1 2 3 4 5 6 7 8 9 10
Difficulty with finding words during conversations	1 2 3 4 5 6 7 8 9 10
Difficulty with expressing yourself	1 2 3 4 5 6 7 8 9 10
Difficulty with short-term memory	1 2 3 4 5 6 7 8 9 10
Difficulty with remembering names	1 2 3 4 5 6 7 8 9 10
Difficulty with forgetting what you read	1 2 3 4 5 6 7 8 9 10
Difficulty with planning ahead	1 2 3 4 5 6 7 8 9 10
Difficulty with organization	1 2 3 4 5 6 7 8 9 10
Neuro-behavioral Symptoms and Issues	**Your Score Mild symptoms .... Severe**
Fatigue issues	1 2 3 4 5 6 7 8 9 10
Difficulty falling sleep	1 2 3 4 5 6 7 8 9 10
Difficulty staying sleep through the night	1 2 3 4 5 6 7 8 9 10
Pain issues	1 2 3 4 5 6 7 8 9 10
Hypersensitivity (light/sound)	1 2 3 4 5 6 7 8 9 10
Headaches	1 2 3 4 5 6 7 8 9 10
Tremors	1 2 3 4 5 6 7 8 9 10
Mood swings	1 2 3 4 5 6 7 8 9 10
Obsessive thoughts	1 2 3 4 5 6 7 8 9 10
Compulsive behavior and/or thoughts	1 2 3 4 5 6 7 8 9 10
Depressed (feeling sad)	1 2 3 4 5 6 7 8 9 10
Difficulty with socializing	1 2 3 4 5 6 7 8 9 10
General anxiety	1 2 3 4 5 6 7 8 9 10
Hyperactivity	1 2 3 4 5 6 7 8 9 10
Agitation symptoms	1 2 3 4 5 6 7 8 9 10
Impulsive behavior	1 2 3 4 5 6 7 8 9 10
Low motivation and apathy issues	1 2 3 4 5 6 7 8 9 10
Frustration issues	1 2 3 4 5 6 7 8 9 10
Anger issues	1 2 3 4 5 6 7 8 9 10
Irritability issues	1 2 3 4 5 6 7 8 9 10

Supplemental Figure 2. NeuroGrow's Concussion Symptom Questionnaire. All symptom ratings (1 to 10) are summed to yield the total score.

EEG-NFB and Brain Coaching

Patients who start the NeuroGrow CRP are scheduled to receive a combination of EEG-NFB (45 minutes) plus brain coaching (45 minutes), twice a week, for 12 weeks. For the EEG-NFB protocol, patients receive z-score brain training with NeuroGuide software (appliedneuroscience.com) (Thatcher, 2013). For their brain coaching sessions, patients meet with their assigned brain coaches twice a week to receive brain training and life coaching (to improve their diet, exercise, sleep, and stress management with meditation).

Brain coaches at NeuroGrow have at least a bachelor's degree in neuroscience or psychology, undergo extensive training from the neurologist, and pass two in-house exams (written and oral) before they can start seeing patients under the supervision of the neurologist. The overall role of the brain coach is to provide positive feedback and encouragement to patients (who are often overwhelmed by their physical and neurocognitive symptoms of PCS), to guide them to perform challenging brain training games, and to encourage them to adhere to healthy lifestyle choices. The specific details of their personalized treatment protocols, ordered by the neurologist, aim to address the specific symptoms each patient suffers from – in order to help them improve their day-to-day function, have a better quality of life, and return to their full pre-TBI capacity.

Patients whose neurocognitive test results indicate problems with executive function are given time-management skills training, including specific help with organizing their daily responsibilities and activities. Patients with memory or other cognitive deficits are given appropriate online brain-training assignments (www.happy-neuron.com) that are monitored by their brain coach. Patients with stress and anxiety are taught breathing exercises and are trained to slow their breathing to a final rate of six breaths per minute for 15-20 minutes. For meditation training, patients interested in smartphone apps are introduced to the headspace (www.headspace.com) and/or calm (www.calm.com) apps. Patients interested in using a biofeedback device for meditation are introduced to the Muse biofeedback device (www.choosemuse.com). Once patients are comfortable meditating using these methods, they may advance to transcendental meditation. Patients with severe depression or post-traumatic stress disorder are referred to health care professionals.

With regard to diet, patients are encouraged to follow a Mediterranean diet, which consists of regular consumption of fruits, vegetables, nuts, whole grains, and olive oil, with fish eaten two to three times a week (Trichopoulou, Costacou, Bamia, & Trichopoulos, 2003; Willett et al., 1995). All patients are instructed to take an omega-3 fatty acid supplement containing between 1000-1500 mg/day of DHA+EPA for the duration of the program (no specific brand of supplement is recommended). With regard to exercise, patients are advised to slowly and safely work up to 45 minutes of vigorous exercise four times per week, doing an activity (or sport) they enjoy. This recommendation is based on the United States Department of Health and Human Services 2008 Physical Activity Guidelines (Office of Disease Prevention and Health Promotion, 2017). Patients with a sedentary lifestyle and vascular risk factors are given the option to undergo cardiopulmonary fitness testing and to work with a certified exercise physiologist to improve their fitness. Patients are monitored, through weekly conversations with their brain coach, and are encouraged to be positive and to increase their level of exercise and RLAs.

Assessing Patient Progress

Mid-way through the program, patients repeat their NeuroCognitive Evaluation (which includes objective testing and a series of questionnaires) and their qEEG brain mapping. Patients then meet with the neurologist to discuss the results, and their individualized NeuroGrow CRP protocol is adjusted (if needed). Because this mid-program evaluation did not take place at equivalent program time points for all patients included in this analysis, the mid-program test results were not included in this study. After program completion, patients take the NeuroCognitive Evaluation and qEEG for a third time. They then meet with the neurologist to review their progress. Based on the findings in their objective tests, responses to questionnaires, and their ability to function well in their daily life, the neurologist will make specific recommendations regarding further brain training, medication changes, or other interventions that could help them gain full recovery from their concussion symptoms (if this has not yet been achieved).

Statistical Analysis

For each patient, both their pre- and post-treatment scores for a given cognitive test were discarded if either score was defined as an 'invalid result' by test criteria. All *t*-tests performed in this study were paired and 2-tailed, and they were calculated using Microsoft Excel 2016. For the pre-post analyses used in this study, $m = 15$ (14 CNS VS domains and the ESS), and the Bonferroni-corrected $\alpha = 0.05/15 = 0.0033$. The ESS pre-post analysis includes only the adult patients in the study. Effect sizes for *t*-tests reported in this analysis are Cohen's d_z (effect size for paired differences), and they were calculated as in (Lakens, 2013). Standard benchmarks were used to define small (≥0.2), medium (≥0.5) and large (≥0.8) effect sizes (Chomycz & Schmidt, 2016).

Reliable Change (RC) calculations were made using the Jacobson-Truax method (Jacobson & Truax, 1991). If RC ≥ 1.96, a patient's change in test score is considered to be "reliable" in the sense that a change of that magnitude would be unlikely to be observed if the true score had not changed. The value of 1.96 is used because if there were no change in scores, 95% of differences would be expected to have an RC of less than or equal to +/- 1.96 (Jacobson & Truax, 1991). The measure of test-retest reliability utilized for these calculations was the Intraclass Correlation Coefficient (ICC) from CNS VS domain scores for test #1 to test #3 from the publication: (Littleton, Register-Mihalik, & Guskiewicz, 2015).

These formulas were used to calculate RC:

$$SE_{meas} = SD_{normative} \times \sqrt{1 - ICC}$$

$$S(diff) = \sqrt{2(SE_{meas})^2}$$

$$RC = \frac{(post\ score) - (pre\ score)}{S(diff)}$$

In order for a score improvement to be considered both reliable and clinically significant, an individual's score must also change from the "abnormal" to the "normal" range (Jacobson & Truax, 1991). The "abnormal" range was defined as a CNS VS test score more than 2 *SD* below the normative mean (score < 70), and the

"normal" range was defined as a test score within 2 *SD* of the normative mean (score ≥ 70) (Chomycz & Schmidt, 2016). The normative mean (*M* = 100) and normative standard deviation (*SD* = 15) were from CNS VS publications ("CNS Vital Signs brief interpretation guide," 2017).

The fixed-effects model of Neurocognition Index scores included 26 total tests (*m* = 26). Therefore, for this experiment the Bonferroni-corrected α = 0.05/26 = 0.0019. This modeling was performed using Stata software (version 15; College Station, TX, USA).

Results

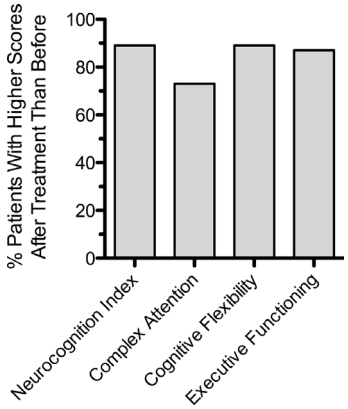
Duration of the Concussion Recovery Program

All patients included in this study were informed that the NeuroGrow CRP is a 12-week program, with two sessions of EEG-NFB and brain coaching each week (for a total of 24 sessions each). However, not all patients complied with these recommendations. The average number of NFB sessions completed during the NeuroGrow CRP by patients in this study was 23 (*SD* = 6), and the average number of brain coaching sessions completed was 20 (*SD* = 8). The average total length of time spent in the program was 19 weeks (*SD* = 12 weeks). The decision to end the program was made by the patient or, for children, by the patient's parent or guardian.

CNS VS Neurocognition Index Scores Improve After NeuroGrow CRP Treatment

The Neurocognition Index (NCI) is the summary output score for the CNS VS suite of tests. The NCI has been shown to be sensitive to patients' degree of brain injury and extent of recovery (Gualtieri & Johnson, 2008), and it is the primary outcome measure for this study. The mean NCI score before treatment was 85.3, which is in the "Low Average" range defined by CNS VS (Table 2; Figure 2). After treatment, the mean NCI score was 95.8, which is within the "Average" range. The difference in patients' NCI score from pre- to post-treatment was evaluated by paired *t*-test, and the results for the NCI and other tests are shown in Table 2. The average change was a significant improvement in score of 10.6 points (*p* = .0001), with a medium effect size. For most patients in this study (89%), their post-treatment NCI score was higher than their pre-treatment score (Figure 3).

Figure 3. Patients with higher CNS VS scores after the NeuroGrow CRP than before. For the CNS VS domains most relevant to concussion/mTBI, the % of patients with higher after-treatment than pre-treatment scores are shown.



For this pilot study of the NeuroGrow CRP, a fixed effects model was used to evaluate the change with treatment, as well as factors that might influence patients' degree of change in NCI score with treatment. The factors considered were age, gender, length of time from concussion to start of program, total weeks spent in the program, total number of NFB sessions, total number of brain coaching sessions, and pre-treatment NCI score. Each of these variables was interacted with the treatment indicator (*i.e.* pre- versus post-treatment), so that their coefficients represent differences in predicted change between pre- and post-treatment associated with that variable. For NCI, the coefficient on treatment was positive and significant (*b* = 10.5; *p* = .0017), indicating that patients' scores were predicted to improve after treatment. Only two of the interactions between treatment and other variables had significant coefficients in the model. The pre-treatment NCI score coefficient was both significant and negative (*b* = -0.389; *p* = .0002), which indicates that, holding all other variables constant, patients who had higher (better) scores on the pre-treatment NCI were predicted to have a smaller change in NCI score than patients with lower pre-treatment NCI scores. The coefficient for total weeks spent in the program was also significant and negative (*b* = -0.952; *p* = .0002). This indicates that patients who spent longer in the program were predicted to have smaller increases in NCI score than patients who spent fewer weeks in the program.

Score Improvement After NeuroGrow CRP Treatment on the CNS VS Domains that are Most Sensitive to MTBI

The CNS VS domains Complex Attention, Cognitive Flexi-

Table 2

Patient Scores Were Improved After NeuroGrow CRP Treatment Compared to Before Treatment for Most Measures

	n	Pre-Treatment Score *M* (*SD*)	Post-Treatment Score *M* (*SD*)	Difference M_d (SD_d)	*t*	*p*	Effect Size (d_z)
CNS VS domains most relevant to concussion/mTBI							
Neurocognition Index	45	85.3 (20.0)	95.8 (18.8)	10.6 (16.5)	4.30	.0001*	0.64
Complex Attention	45	86.1 (27.8)	103.2 (11.8)	17.2 (22.3)	5.16	<.0001*	0.77
Cognitive Flexibility	46	85.1 (25.4)	103.2 (18.1)	18.1 (16.0)	7.70	<.0001*	1.14
Executive Functioning	46	85.9 (25.3)	103.9 (17.6)	18.0 (16.0)	7.62	<.0001*	1.12
CNS VS domains less directly relevant to concussion/mTBI							
Composite Memory	45	89.4 (18.4)	95.9 (21.3)	6.5 (16.8)	2.58	.0133	---
Verbal Memory	45	86.7 (18.8)	97.1 (20.3)	20.8 (39.1)	3.57	.0004*	0.53
Visual Memory	45	95.6 (14.6)	96.5 (20.2)	0.9 (17.4)	0.34	.7341	---
Psychomotor Speed	46	91.5 (17.5)	98.2 (17.5)	6.7 (12.2)	3.73	.0005*	0.55
Reaction Time	45	80.9 (30.1)	91.1 (24.7)	10.2 (17.8)	3.86	.0004*	0.57
Processing Speed	46	99.9 (16.0)	106.5 (16.2)	6.6 (15.4)	2.89	.0060	---
Working Memory	40	97.9 (19.6)	107.5 (11.0)	9.6 (17.5)	3.47	.0013*	0.55
Sustained Attention	39	99.3 (14.5)	106.0 (13.4)	6.7 (12.3)	3.38	.0017*	0.54
Simple Attention	44	89.8 (24.9)	97.3 (15.9)	7.5 (22.4)	2.23	.0309	---
Motor Speed	46	89.6 (15.6)	93.7 (15.4)	4.1 (10.6)	2.64	.0114	---
Tests for which a decrease in score indicates improvement							
ESS[a]	32	8.6 (4.2)	6.9 (3.6)	-1.7 (3.8)	-2.50	.0180	---

Note. T-tests were paired (pre- to post-treatment) and 2-tailed. Cohen's d_z is effect size for paired differences.
[a]ESS: only adult patients are included for this measure
*Significance level after Bonferroni correction: $\alpha_B = 0.0033$

bility, and Executive Functioning are considered by the test manufacturer to be the most sensitive domains to mTBI and concussion ("CNS Vital Signs brief interpretation guide," 2017). For all three domains, the mean score before treatment was in the "Low Average" range, and the mean score after treatment was in the "Average" range, as defined by CNS VS (Figure 2). Paired *t*-tests were used to evaluate the difference between patients' pre- and post-treatment scores, and results are shown in table 2. For all three domains, average change in score after the NeuroGrow CRP was a significant increase in score ($p < .0001$) with a medium or large effect size. The % of patients who scored higher on these domains after treatment compared to before is shown in Figure 3.

Score Changes After Treatment for CNS VS Domains that are Less Directly Relevant to mTBI

The CNS VS suite of tests also includes other cognitive domains that are less directly relevant to concussion/mTBI. Paired *t*-test results for these domains are shown in Table 2. Patients experienced significant improvement in score after the CRP for Verbal Memory, Psychomotor Speed, Reaction Time, Working Memory, and Sustained Attention, with medium effect sizes. For Composite Memory, Visual Memory, Processing Speed, Simple Attention, and Motor Speed, patients did not experience a significant score change after treatment at the Bonferroni-corrected significance threshold of $\alpha_B = 0.0033$.

No Change in ESS Scores After NeuroGrow CRP Treatmen

Before and after the NeuroGrow CRP, patients were also evaluated for level of daytime sleepiness by the ESS (which has been validated for an adult population aged 18-78 (Johns, 1992)). On the ESS, a decrease in score indicates improvement. For the adult patients in the study, the average pre-treatment score was 8.6, and the average post-treatment score was 6.9 (Table 2). The mean change in score was a decrease of 1.7 points, which was not significant after Bonferroni correction ($p = 0.018$).

Reliable Improvements of Clinical Significance for Relevant CNS VS Domains

All methods of measurement contain some amount of variability due to error. For repeated measurements, in some cases score improvement would be expected merely from taking a given cognitive test for the second time. For a particular measurement tool, it is possible to distinguish reliable change in score from measurement error if the expected degree of test-retest variability is known. There are published values of test-retest reliability available for the Complex Attention, Cognitive Flexibility, and Executive Functioning domains of the CNS VS (Gualtieri & Johnson, 2006; Littleton et al., 2015). In the more recent of these studies, Littleton and colleagues included test-retest reliability values that compare the third time taking these tests to the first (Littleton et al., 2015) (which was also the case for patients in the present study), and these values were used to calculate the Reliable Change (RC) for these domains (see Methods). Although the study by Littleton considered healthy college-aged subjects who took tests between 6 and 11 days apart, a previous study found that test-retest reliability for CNS VS is higher (better) in neuropsychiatric patients compared to healthy controls (Gualtieri & Johnson, 2006), and it is therefore reasonable to assume that the test-retest values from the Littleton study are not an underestimate for the present study.

By the RC measure, 27% of patients in this study experienced reliable improvement after treatment on Complex Attention, 30% on Cognitive Flexibility, and 33% on Executive Functioning. No patients in the study experienced reliable deterioration (a decrease in score by at least the RC). For a patient to experience reliable improvements of clinical significance, they must have started the program with a score within the "abnormal range" for a particular test (Jacobson & Truax, 1991) (see Methods). For this subset of patients who began the program with abnormal scores, 70% (7 out of 10) experienced reliable, clinically significant improvement in test score for Complex Attention, 67% (8 out of 12) for Cognitive Flexibility, and 64% (7 out of 11) for Executive Functioning. The remaining patients who began the program in the abnormal range for these test domains did not experience a large enough change in score (either improvement or deterioration) to be considered reliable.

NeuroGrow's In-House Symptom Questionnaires Before and After Treatment

Patients in the NeuroGrow CRP take the "Brain Fitness Calculator" and the "Concussion Symptom Questionnaire" before and after the CRP (Supplemental Figures 1, 2). These in-house measures are used because, to our knowledge, there is currently a gap in the medical literature for validated measures that specifically address the nature and severity of a wide range of symptoms that can affect patients with PCS as well as their brain health and quality of life. In this study, we are reporting descriptive statistics for patients' scores on these measures before and after treatment.

For the Brain Fitness Calculator, a higher score is considered better. Before the CRP, patients in the program had a mean score of 46.1 out of 75 ($SD = 8.7$; $n = 38$). After treatment, patients had a mean score of 54.5 out of 75 ($SD = 9.4$), with an average score increase of 8.4 points ($SD_d = 6.3$). For the Concussion Symptom Questionnaire, a lower score is considered better. Before the CRP, patients had a mean score of 156.7 out of 350 ($SD = 65$, $n = 35$). After treatment, patients had a mean score of 111.9 out of 350 ($SD = 58.9$), with an average score decrease of 44.8 points ($SD_d = 55.7$).

Discussion

There is currently no consensus in the field on an effective treatment for PCS (Blennow et al., 2012; Hadanny & Efrati, 2016). This is likely due, in part, to the variability and severity of concussion symptoms among these patients. Like other chronic conditions such as fibromyalgia (Lawson, 2008), PCS is a complex disorder that requires a multi-disciplinary treatment strategy. Although there is no agreed-upon "best" treatment for PCS, many therapeutic techniques have shown promising results for at least some groups of patients (Bailes & Patel, 2014; Duff, 2004; Leddy et al., 2010; Munivenkatappa et al., 2014; Ponsford et al., 2002; Reddy et al., 2014; Surmeli et al., 2017; Thompson et al., 2013; Tinius & Tinius, 2000; Walker et al., 2002; Zorcec et al., 2011). The NeuroGrow CRP protocol combines promising methods from the medical literature into a multi-disciplinary, individualized treatment strategy for patients suffering from PCS. The goal of this program is to treat *all* of a patient's PCS-related symptoms under the care of a single physician, so that no patient "slips through

the cracks" with fragmented care due to lack of communication between specialists. Two relevant components of the NeuroGrow CRP are EEG-NFB and brain coaching.

EEG-NFB, which seeks to normalize brain wave patterns, has shown promising results for a wide range of neurological conditions (Niv, 2013). A recent meta-analysis on EEG-NFB for children with ADHD determined that EEG-NFB was as effective as standard treatments (psychotherapy or medication) for hyperactivity/impulsivity symptoms, and these effects were maintained six to twelve months beyond the end of treatment (Van Doren et al., 2019). There is also evidence that adults with ADHD benefit from EEG-NFB (Mayer, Blume, Wyckoff, Brokmeier, & Strehl, 2016). Further, EEG-NFB has been associated with reduction of symptoms in anxiety, depression, and PTSD (Niv, 2013; van der Kolk et al., 2016; White et al., 2017). Since attention, concentration, anxiety, depression, and PTSD are common features of PCS, it is reasonable to predict that EEG-NFB could be helpful for treating patients with PCS, and there is evidence in support of this (Duff, 2004; Munivenkatappa et al., 2014; Reddy et al., 2014; Thompson et al., 2013; Tinius & Tinius, 2000; Walker et al., 2002; Zorcec et al., 2011). A recent study suggests that EEG-NFB alone may be sufficient to improve some symptoms for some patients with PCS (Surmeli et al., 2017). However, given the chronicity, severity, and variable nature of symptoms in patients with PCS, it is unlikely that EEG-NFB can provide a definitive treatment strategy for *all* patients with PCS. As such, the NeuroGrow CRP combines EEG-NFB with another novel approach to treatment of patients with PCS, which we have termed "brain coaching."

Brain coaching has two components, a brain training component and a lifestyle enhancing component. Brain coaches function as enthusiastic trainers to help patients regain their cognitive abilities and to assemble and coordinate their recovery process. Under the direction and supervision of a neurologist, they provide patients with tailored cognitive stimulation for the specific domains that are affected by their TBI (noted on their neurocognitive test results). They help patients to improve their memory, attention, executive function, and processing speed and to exercise more, sleep better, and communicate more effectively with their family members, co-workers, or teachers. Brain coaches receive intensive training on concepts of neuroplasticity, the importance of vascular risk factor modification for improving brain health, and the critical roles of sleep hygiene, diet, exercise, and meditation for enhancing mood and cognitive performance. Brain coaches assist patients with incorporating necessary lifestyle modifications that are needed for better fitness, lower levels of anxiety, and maintaining a positive attitude toward their recovery. With a deep understanding of the neurobiology of changes in the brain with concussion and with neuroplasticity, they provide patients with various hands-on and online brain games that are both engaging and stimulating. They coach patients to become more confident in their cognitive abilities by showing them how they have improved on a weekly basis. They assure patients that the brain has the ability to repair itself and that certain interventions can enhance this process (Cutuli, 2017; Duff, 2004; Erickson et al., 2011; Fotuhi, Do, & Jack, 2012; Francis & Stevenson, 2018; Ghaziri et al., 2013; Muldoon et al., 2010; Munivenkatappa et al., 2014; Nudo, 2013; Tang, Holzel, & Posner, 2015; Wu, Ying, & Gomez-Pinilla, 2004).

The Neurobiological Basis of the NeuroGrow CRP

The NeuroGrow CRP incorporates interventions that have been shown to increase neurogenesis and brain volume (Baptista & Andrade, 2018; Fotuhi et al., 2012; Shohayeb, Diab, Ahmed, & Ng, 2018). Aerobic exercise has been shown to increase BDNF, increase the size of the hippocampus, and improve memory (Erickson et al., 2011; Liu & Nusslock, 2018). Further, there is evidence that mindfulness meditation may increase brain blood flow and volume as well as decreasing anxiety (Tang et al., 2015). A small study found that patients with TBI experienced improvements in QOL that were maintained for at least a year after a mindfulness-based intervention that included meditation (Bedard et al., 2005; Bedard et al., 2003). Omega-3 fatty acid supplementation has been shown to increase synaptogenesis and hippocampal neurogenesis in animal studies (Cutuli, 2017). Higher levels of omega-3 fatty acids are also associated with increased levels of BDNF and improved learning after TBI in rats (Wu et al., 2004). Higher serum concentrations of DHA are associated with better performance on a range of cognitive tasks in humans (Muldoon et al., 2010), and individuals with an anxiety or depression diagnosis have lower levels of omega-3 fatty acids (Larrieu & Laye, 2018). EEG-NFB can also potentially expand brain volume; one study showed frontal lobe brain regions important for attention increase in size after three months of treatment with EEG-NFB (Ghaziri et al., 2013). Thus, it is possible that the neurocognitive improvements experienced by PCS patients who completed NeuroGrow CRP may have been in part due to brain neovascularization, neurogenesis, and synaptogenesis. In future prospective studies, it will be helpful to collect imaging and blood markers for these processes (e.g. brain MRIs or serum BDNF levels) along with the results of neurocognitive testing and questionnaires.

Strengths and Limitations

This pilot study is a detailed retrospective analysis of patient data taken both before and after completion of the NeuroGrow CRP. Strengths of the study include the individualized format of the intervention strategy and the unique combination of NFB and brain coaching that aims to improve the biological repair processes in patients with PCS and emphasizes their quality of life and RLAs. The multi-disciplinary nature of the NeuroGrow CRP could be a reason for its apparent success, including significant improvements with medium-to-large effect sizes for most measures examined. Further, the outcome measures included objective neurocognitive testing by the widely used and validated CNS VS battery of cognitive tests, which is completely computerized and independent of the test administrator.

Main limitations of this study include the relatively small number of subjects (n = 46) and the lack of a control group. Further, we analyzed the neurocognitive data, obtained from CNS VS test results, for children (ages 10 to 17) together with those from adults, despite the fact that concussion can affect the brains of children and adults differently (McKee & Daneshvar, 2015). This decision was made because the NeuroGrow CRP protocol is individualized to each patient's specific (age-appropriate) needs, and because the CNS VS output scores are already age-controlled (based on comparison with normal controls of the same age range). In support of this decision, in our fixed effects model, the interaction between treatment and the variable 'age' did not have

a significant coefficient, indicating that, holding all other variables constant, a patient's age was not predicted to affect their change in NCI score after treatment.

To address these limitations, and to confirm the results of this pilot study, future clinical trials should include a large sample size, a wait-list control group, subgroups with variable doses of intervention (e.g. brain coaching once a week, twice a week, or four times a week), and consider whether patients in different age groups respond differently to treatment. Further, patients should be re-examined at six and twelve months beyond completion of the program to determine the longevity of effects from the program. MRI data from our previous study of a similar multi-disciplinary program for elderly patients with mild cognitive impairment indicated that there could be improvements in hippocampal volume after treatment (Fotuhi et al., 2016). Therefore, including brain imaging data – as well as serum markers for monitoring repair mechanisms in the brain - would also be a valuable addition to future studies of the NeuroGrow CRP (or other rehabilitation programs) for patients with PCS.

Implications for Rehabilitation Counselors:

The findings of this pilot study have several important implications for rehabilitation counselors who work with PCS patients.

- Patients with PCS have "invisible" symptoms, including slow processing speed in handling information, irritability, sad mood, fatigue, or hypersensitivity to light and sound. These symptoms can be quite frustrating, especially since employers, physicians, or family members of the patient may not take their complaints seriously. Over time, patients become increasingly frustrated with their lower level of performance and may develop chronic anxiety or depression. As such, rehabilitation counselors need to obtain a full set of information that includes psychological, neurological, medical, vocational, and family issues. Successful treatment of PCS patients requires a comprehensive assessment and multi-disciplinary approach that addresses all of their symptoms and issues and emphasizes having a positive attitude toward full recovery.
- Rehabilitation counselors need to help PCS patients to improve their cognitive abilities, not only through standard cognitive training modules, but also through RLAs that target different cognitive domains and improve their sense of well-being (Thomas et al., 2015). For example, taking dance, painting, or pottery classes can help patients learn the limits of their capabilities and work to enhance their performance in a comfortable and fun environment. Similarly, engaging in fishing, cooking, photography, or other hobbies they enjoy can boost their confidence as they realize they can get better with practice. RLAs can help them improve their vocational outcome, mood, and overall life satisfaction (Thomas et al., 2015).
- Rehabilitation counselors need to encourage their patients to improve their diet and exercise habits. Improving physical fitness and eating a Mediterranean diet can enhance the repair mechanisms in the brain and contribute to better mood, sleep, and cognitive performance (Fotuhi & Antoniades, 2013; Gomez-Pinilla & Kostenkova, 2008; Phillips, 2017; Wu, Ying, & Gomez-Pinilla, 2013). Engaging in safe physical activities such as riding a stationary bike can provide an opportunity for patients to improve their physical fitness without the risk for falls. Then, if possible, they can engage in sports such as biking, tennis, or swimming to become stronger and more confident. Rehabilitation counselors should emphasize the benefits of stress reduction with slow breathing techniques, meditation, or yoga. These interventions, as well as EEG-NFB (when available), may improve patients' sleep, cognitive abilities, and personal relationships.

Summary

This retrospective study is an analysis of objective and subjective data from 46 patients with PCS before and after completion of the NeuroGrow CRP. After the program, patients experienced significant improvements in most neurocognitive test scores. This includes improvement in overall cognitive function (as measured by the CNS VS summary score of Neurocognition Index), and more specifically in the three CNS VS domains considered to be the most sensitive to mTBI by the test publisher (Complex Attention, Cognitive Flexibility, and Executive Functioning). For the subset of patients who scored in the "abnormal" range before treatment, at least 64% experienced reliable and clinically significant improvement in these scores. Large clinical trials with appropriate control groups are needed to confirm our preliminary findings.

Disclosure Statement

Author MF is the primary neurologist, and all other authors are either employed by or are consultants with the NeuroGrow Brain Fitness Center, which is a private neurology practice in Northern Virginia. This work was not supported by a grant or other funding from a public, not-for-profit, or commercial funding agency.

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