Developing the Standard of Care for Post-Concussion Treatment: Neuroimaging-Guided Rehabilitation of Neurovascular Coupling

Benjamin H. Wing\textsuperscript{1,2}; Braden J. Tucker\textsuperscript{1,4}; Alina K. Fong, PhD\textsuperscript{1,3}; E. Bruce McIff, MD\textsuperscript{1,2}; Mark D. Allen, PhD\textsuperscript{1,2}
\textsuperscript{1}Cognitive FX, Provo, UT
\textsuperscript{2}Notus Neuropsychological Imaging, Orem, UT
\textsuperscript{3}Utah Valley Regional Medical Center, Provo, UT
\textsuperscript{4}Case Western Reserve University School of Medicine, Cleveland, OH

ABSTRACT

Objective. Emerging research proposes the imbalance between microvascular supply and metabolic demand as a contributing factor in the pathophysiology of mild traumatic brain injury (mTBI). Prolonged effects on the dysregulation of neurovascular coupling (NVC) may explain persistent symptomatic models such as Post-Concussion Syndrome (PCS). Increased knowledge of what we refer to as Neurovascular Uncoupling (NVU) provides a template for establishing a new concussion treatment standard in the assessment and therapeutic guidance of concussion.

Participants & Methods. The degree and localization of NVU was statistically contextualized against a normative-based atlas in 270 concussed patients using Functional NeuroCognitive Imaging\textsuperscript{TM} (fNCI) to establish pre-treatment benchmarks and methodically guide neurotherapy. Conventional and fNCI-directed measures were used to evaluate post-rehabilitative outcomes.

Results. fNCI was successful in identifying regions of NVU unique to each patient’s brain and concussion profile. Longitudinal objective outcome measures demonstrated timely and lasting improvement of NVC functioning in a significant majority of patients.

Conclusions. We present practice-based evidence supporting the clinical administration of fNCI with particular efficacy in the neurorehabilitation of mTBI. We advocate the reliability of fNCI in assessing severity and localization of NVU, and promote its use in the therapeutic guidance and neurorehabilitation of mTBI. We further support the continual exploration of other potential pathophysiological involvement in this complex brain injury.

KEYWORDS

Mild traumatic brain injury (mTBI), concussion, post-concussion syndrome (PCS), regional cerebral blood flow (rCBF), neurovascular coupling (NVC), neurovascular uncoupling (NVU), enhanced performance in cognition\textsuperscript{TM} (EPIC), functional magnetic resonance imaging (fMRI), clinical fMRI, blood oxygen level dependent (BOLD) signals, functional neurocognitive imaging\textsuperscript{TM} (fNCI), severity index score (SIS), post-concussion symptom scale (PCSS), neurorehabilitation, treatment standards, accelerated improvement, longitudinal outcome
1. INTRODUCTION

1.1 MILD TRAUMATIC BRAIN INJURY

Recent reports by the Center for Disease Control (CDC) indicate that traumatic brain injury (TBI) has increased by 60% in the general population from 2001-2010 with mild TBI (mTBI) composing approximately 80% of those events (Management of Concussion/mTBI Working Group, 2009).

Likewise, Armed Services report nearly 348,000 traumatic brain injuries since 2000 with 82.3% classified as mTBI (Defense and Veterans Brain Injury Center, 2016). This significant increase in mTBI diagnosis is a result of improved awareness of its epidemiology, etiology, presentation, sequela, and even trends toward more aggressive play in sports and other activities (Clay et al., 2013). Consequently, increased health care demand has led to an urgent need for valid guidelines for accurately assessing and diagnosing this complex injury (Carney et al., 2014). Recently, extensive efforts have been made to understand the diagnosis, prognosis, and treatment of mTBI, as well as the persistent underlying physiological changes that may occur in post-concussion syndrome (PCS), such as neurovascular signaling disruptions that take place within cortical micro-structure. However, most current treatment approaches do not incorporate advanced scientific findings of the underlying causes of persistent mTBI dysfunction into rehabilitative practice, but rather rely on traditional strategies that are largely focused on reducing overt symptoms.

Current guidelines for treatment of acute mTBI center on limiting physical and cognitive activity while reducing exposure to symptom-aggravating stimuli until it is deemed that the patient has returned to normal function (Clay et al., 2013). In many cases, the treatment course may last weeks, months, and years. For these more chronic symptoms, the standing recommendation for treatment of post-concussion conditions is a symptoms-based approach (Management of Concussion/mTBI Working Group, 2009).

In other words, clinicians address each symptom individually, as if they were an independent condition, and often employ pharmacological and medical therapy when rest itself does not mitigate the symptoms. This approach can prove problematic for many mTBI patients because of their increased susceptibility to adverse side effects of the medication to treat their symptoms, often worsening overall symptom presentation in many cases (Chapman et al., 1999). A salient example of this problem is the common diagnosis and subsequent psychopharmacologic treatment of psychiatric symptoms diagnosed post-mTBI. Often, the side effects of these medications mimic and exacerbate ongoing concussion symptoms (Warden et al., 2006).

Additionally, the diagnosis of Axis I psychiatric conditions is highly questionable, as many of these patients have no premorbid history of psychiatric illness, and developed these symptoms only after struggling with the sequelae for months (McAllister & Arciniegas, 2002; Warden et al., 1997). Although the current treatment methods promote patient recovery from some mTBI symptoms, this approach may fail to address the underlying etiology and pathophysiology of concussions that results in longitudinal alterations in cognitive, occupational, emotional, and neuromuscular function (Warden et al., 2006).

Consequently, a standard for care that addresses and treats the underlying
pathology is needed for effective treatment of post-concussion symptoms as opposed to masking the condition by treating individual presentations.

1.2 NEUROVASCULAR COUPLING

Recent scientific investigations on the effects of concussion suggest that disruptions to neuronally-triggered regional cerebral blood flow (rCBF) may account for a significant portion of PCS symptoms (Ellis et al., 2016; MacFarlane & Glenn, 2015).

Normal brain functioning relies on highly responsive mechanisms of blood flow regulation that are sensitive to the immediate and shifting demands for steady glucose metabolism throughout the brain (Giza & Hovda, 2001). Anything less than precise neurovascular coupling (NVC) between neural activity and blood flow may result in obvious cognitive and physical deficits (Mikulis, 2013). Although permanent gross structural brain damage is not observed in concussion/mTBI (by definition), there is clear evidence for long-term disruption of NVC, associated with measurable neurocognitive dysfunction (da Costa et al., 2016; Meier et al., 2015; Mutch et al., 2015; Wang et al., 2015; Bartnik-Olson et al., 2014) and physical dysfunction (Kozlowski et al., 2013; Leddy et al., 2013) typical in PCS symptomology. We refer to this phenomenon as Neurovascular Uncoupling (NVU).

Given the key role that NVU is likely to play in PCS, effective treatment should include 1) an objective neuroimaging method for detecting NVU in the brain, and 2) an informed rehabilitation protocol with advanced techniques for restoring normal NVC. We present here data from a large sample of mTBI patients assessing the effectiveness of one specific treatment program, Enhanced Performance in Cognition™ (EPIC) treatment, which employs a novel, evidence-based system of atypically aggressive NVC recovery therapies.

Functional magnetic resonance imaging (fMRI) has been used extensively over the last two decades as the dominant research tool for understanding human brain function. fMRI is often described as a method that detects ‘brain activity.’ However, a more accurate description of fMRI would be that it detects efficiency in NVC. Although fMRI does not directly measure neural activation, it has nonetheless proven to be a highly reliable tool in brain function mapping, given the precise coupling that normally exists in the healthy brain between neural activity and the blood oxygen level dependent (BOLD) signal that is detected by fMRI (Bandettini, 2012). However, due to the very fact that fMRI is a more direct measure of NVC efficiency than neural activity itself, it is currently the most ideal imaging tool to measure dissociations between NVC and what is otherwise normal brain cell functioning in unhealthy brains, specifically as found in PCS.

Given the special nature of fMRI with regard to mTBI dysfunction, many high-quality research studies over the last decade have used fMRI to investigate neurocognitive effects of concussion (Keightley et al., 2014; McDonald et al., 2012; Slobounov et al., 2010; Chen et al., 2008), and, to a limited extent, treatment outcomes (Koski et al., 2015; Leddy et al., 2013). However, the fMRI method as standardly employed in scientific research lacks essential features necessary for clinical assessment: 1) a concurrently validated, reliable, and objective standardized protocol appropriate for the scanning environment, and 2) a clinically acceptable normative-
based contextualization procedure for appropriate individualized patient assessment (Ellis et al., 2016).

1. METHODOLOGY

2.1 FUNCTIONAL TASK BATTERY

Our unique functional NeuroCognitive Imaging™ (fNCI) assessment protocol combines the validity of conventional neuropsychologic testing standards with the reliability and objectivity of informational data output provided by fMRI. The testing battery underwent iterative pilot testing to ensure concurrent validity, reliability, objectivity, and suitability for the scanning environment (Allen & Fong et al., 2010; Allen & Fong, 2008a; Allen & Fong, 2008b).

The functional task battery, Notus NeuroCogs™, is comprised of six neuropsychologic test adaptations: the functional Matrix Reasoning Test™ (f-MRT), the functional Trail Making Test B™ (f-TMTB), the functional Picture Naming Test™ (f-PNT), the functional Face Memory Test™ (f-FMT), the functional Verbal Memory Test™ (f-VMT), and the functional Verbal Fluency Test™ (f-VFT). Each of the six tasks includes eight Test Phases presented in alternating fashion with Rest Phases, in which the subject is asked to silently count from 1 to 10. Compliance monitoring is performed at intervals during each task. Operative descriptions are outlined below:

The f-MRT tests non-verbal problem solving using a 3x3 array of visually complex figures with one figure missing. The subject is then instructed to select the best match for the missing figure from among four “candidate” figures by pressing a designated button.

The f-TMTB measures cognitive flexibility by presenting a virtual connect-the-dots tasks using a button pad response system.

Randomly arranged numbers and letters are displayed on a screen and the subject must locate and connect each series of numbers and letters in ascending order while alternating back and forth between the two character types.

The f-PNT assesses semantic object recognition by displaying line drawings of common objects for a period of 1.5 seconds each. Subjects are instructed to silently identify each object upon presentation.

The f-FMT investigates long-term memory. Subjects are instructed to memorize colored photographs of unfamiliar faces and informed that they will be required to identify some of the faces at a later time. Twenty faces are presented twice in 2 random orders for three seconds each during scanning. Recognition accuracy is recorded on a post-scan test.

The f-VMT analyzes short-term verbal memory. For each test run, the subject views a series of eight common words for one second each and is instructed to silently memorize the words as they appear. Subjects are given 12 additional seconds after all words have been presented to recall as many as possible.

The f-VFT is a letter-based fluency test. The subject is instructed to silently generate as many unique words as possible (excluding proper names or variants of the same word) within a 20-second time limit using a given first letter.

2.2 NORMATIVE ATLAS

In order to further support the reliability of our testing battery and employ its clinical application, we utilized a group-summary analysis approach, where single-subject NVC is compared against normative datasets.

The fnCI assessment protocol was initially performed on a population comprised of 59 normative reference volunteers (27 male, 32
female) between the ages of 19-57 years old (Mean = 30.1, σ = 8.5). Edinburgh Handedness Inventory analysis found right-hand dominance in 91.5% of subjects. Majority of participants within this population were Caucasian (74.6%), with the remaining being: Hispanic (11.8%), Asian (10.2%), and African American (3.4%). Reference subjects all spoke English as their first language and had at least one year of higher education (Mean = 14.3, σ = 2.9).

Data analysis revealed 57 specific activation regions found to be task-associated with the Notus NeuroCogs™ task battery. Additionally, these regions of interest were found to possess a normal distribution of functional NVC efficiency amongst reference subjects. This distributive property formulated a three-dimensional activation standard, or normative atlas, which was later used to statistically contextualize both severity and localization of NVU in 270 concussed patients.

2.3 CLINICAL FUNCTIONAL NEUROCOGNITIVE IMAGING

Although traditional uses of fMRI and other advanced neuroimaging methods have been employed primarily for research purposes or preoperative functional mapping, we are rapidly approaching the standardized integration of these advanced imaging techniques in clinical evaluation [Zhang et al., 2009; Matthews, Honey, & Bullmore, 2006]. But several key limitations have hindered the universal application and establishment of clinical fMRI practice. For the scope of this paper, we aim to present the two most general, yet major, limitations and briefly discuss our standardized approach to address their limiting effects on fNCI-specific data retrieval, contextualization, and clinical application.

In recent years, questions within the scientific community have been raised regarding the clinical reliability of fMRI because of rising skepticism towards BOLD signal stability. Skepticism revolves around the belief that fMRI data output (BOLD signal activation) is both unreliable and irreproducible (Plichta et al., 2012; Bennett & Miller, 2010). To provide a better framework that enforces BOLD signal stability, researchers have scientifically discovered a strong relationship between fMRI reliability characteristics and paradigm standardization (Ellis et al., 2016; Pichta et al., 2012). Through years of extensive pre-testing, Notus NeuroCogs™ has been examined for concurrent validity, reliability, objectivity, and suitability within the scanning environment using a standardized administration protocol (Allen et al., 2012; Allen, Wu, & Bigler, 2011; Allen et al., 2011; Allen & Fong, 2008a; Allen & Fong, 2008b). In addition, our standardized functional task battery has been directly assessed for test-retest stability in a sample of 14 healthy controls to date, yielding a correlational average of \( r = 0.859 \) (StDev = 0.0904) amongst 57 task-associated regions (data specifics not shown).

The other well known, reoccurring argument made against clinical fMRI questions the appropriateness and sufficiency of statistical corrections made during fMRI data analysis (Eklund et al., 2012). Notably, all fMRI analyses include complex chains of statistics, but there is nowhere in our statistical pipeline that includes the type of inferential process(es) that would be subject to the concern of correcting for false positives. Avoiding these clinical criticisms associated with experimental methods of null hypothesis testing, our statistical contextualization
approach removes all concern through individualized analysis of raw patient data.

Our strict adherence to raw data completely sidesteps the major issue surrounding inferential analyses (i.e. threshold-based significance testing), and places fNCI more in terms of fMRI’s objective implementation within its presurgical application. The cost of this clinically acceptable methodology, however, requires laborious work, employing a qualified neuroanatomist to assess both structural and functional variability unique to each brain, to ensure accurate identification of task-associated regions, thereby equating appropriate clinical relevance.

Using the same, standardized administration presented to normative references, each patient was scanned using fNCI to establish pre-treatment benchmarks used in measuring ultimate therapeutic effectiveness. Activational data output was projected against the normative atlas to statistically contextualize degree of NVU present in any given brain region for each patient. Furthermore, regional NVU breakdown provided target regions of interest for neurorehabilitative efforts. This individualized localization of neurovascply-uncoupled regions supports the clinical appropriateness of fNCI-directed treatment.

2.4 EPIC TREATMENT

In addition to standardized test administration, normative-based assessment, and individual, image-guided measurements, our EPIC treatment exploits the latest knowledge of NVC and its role in PCS by integrating three fundamental rehabilitation facets for each patient: Prepare, Activate, Rest. Specific therapeutic activities included in each of these three phases of EPIC treatment are the product of extensive research, clinical experience, screening, and empirical testing. They address a wide range of cognitive, sensory and physical functions.

The key to success, however, is not necessarily the therapies themselves, but the manner in which the therapies are applied (i.e., timing and order). For example, a carefully guided rotation between physical/cardio challenge and cognitive or sensory processing challenge is a central feature in restoring the timed pairing between rCBF and regional neural firing.

Our multidisciplinary team was successful in restoring pre-traumatic NVC through the cyclical application of these rehabilitative principles supplied in tandem with the benefit of appropriately timed neurocognitive exercise (Thomas et al., 2015; Majerske et al., 2008).

A multi-method approach was also employed to avoid overexertion of brain regions with severe NVU. Accordingly, cyclical brain training aimed to strengthen surrounding neural correlate systems, which, in turn, support the more severely uncoupled regions. Sustained therapy over a multi-day period was shown to promote accelerated and longitudinal restoration of pre-traumatic NVC.

2.5 REHABILITATIVE MEASUREMENTS

NVU values were computed for each individual patient and reported as Severity Index Scores (SIS). In addition to the objective SIS measurement, we retain the use of Post-Concussion Symptom Scales (PCSS)—an existing neurocognitive assessment standard in the form of a self-report survey completed before, during, and after treatment—to supplement our measurement of the effectiveness of fNCI-directed treatment.
Severity Index Scores (A) and Post-Concussion Symptom Scales (B) are graphically reported as shown above. A) Healthy, Borderline, Mild, Moderate, and Severe levels of neurovascular uncoupling can be visualized. B) Various categorical symptoms can be individually observed in addition to the PCSS Total Index Score over the sustained, multi-day treatment period.

2. RESULTS

3.1 PATIENT OUTCOMES

Data collection and analysis confirmed the effectiveness of fNCl-directed treatment in accelerated concussion rehabilitation. Quantitative improvement was observed on both objective fNCl measurements and subjective symptom report measurements after an average of 4.1 days of EPIC treatment. Average pre- and post-treatment measurements are reported for a sample of 270 concussed patients.

Average pre- and post-treatment scores reported under both objective (A) and subjective (B) measurements and are reported to graphically visualize average patient outcome.
3.2 ASSESSMENT OF DEMOGRAPHIC VARIABLES ON OUTCOMES

Considering a wide variety of concussion profiles with regards to age, sex, mode of injury, and time since injury, our EPIC treatment has also been shown to be extremely effective under both objective and subjective measures.

Concussion profiles vary greatly amongst patients considering age (A), sex (B), mode-of-injury (C), time since injury (D), and other demographical characteristics. Patient outcomes under these varying profiles are reported.

3.3. Improvement Outcomes

Improvement, in a broad sense, was been observed in 99.6% and 99.2% of our patients under objective and subject measurements, respectively. But the degree of improvement varied across a wide spectrum of percent differences (Range = 3.24 to 157.0%). Consequently, to address this complication, we established incremental improvement thresholds and report the total percentage of our patients that meet and/or exceed such thresholds. Average improvement is also graphically visualized.
For many patients, the matter of significant improvement varies based-upon the quality-of-life-impact their persistent symptomatic profile manifests post-concussion. As such, our patients have reported a “significant improvement” across a spectrum of percent differences. To adequately report improvement thresholds, a spectrum of improvement percents are graphically presented against percents of our patient population who have improved by such thresholds or greater. Improvement thresholds and their percentages can be observed for both SIS and PCSS measures.

3.4. Short-Term Outcome Comparison

A random sample of 27 patients who underwent EPIC treatment was generated to visually characterize the original pool of 270 patients. This sample was reported against a group of 27 patients who, at the time of initial scanning, opted to delayed treatment and were rescanned at a later date.

Additionally, it was comparatively reported against a sample of 13 healthy controls that were scanned in order to assess test-retest reliability of the fNCI method. The random sample accurately represents improvement trends reported above (refer to Image 4), observing improvement in 100%
of patients, with an average of ~70% improvement amongst the treated patient sample (73.1% of which returned to within-normal-limits post-treatment. In comparison, 65.4% of patients who did not receive treatment saw spontaneous improvement, averaging 18.4% improvement (only 3.8% of which spontaneously returned to within-normal-limits.

### Image 5

Random sampling of treated patients, non-treated patients, and healthy controls accurately represents total patient outcomes, and further supports the efficacy of positive short-term results using fNCI-directed treatment. All SIS scores within the denoted range (area shaded green) are considered within normal limits.

Note: The healthy control mean (SIS = 0) elucidates the possibility of negative SIS values. These values are still considered to have fallen within normal limits.

#### 3.5 LONGITUDINAL OUTCOMES

Recovery in acute models of mTBI is often unpredictable. For those injuries that progress into persistent cases, research findings allude to the pathophysiological misalignment in default NVC efficiency.

Accordingly, a rehabilitative approach that promotes the restoration of default NVC efficiency should, therefore, expect longevity of positive outcomes in PCS. As expected, longitudinal outcomes for fNCI-directed treatment report sustained rehabilitative outcomes in follow-up scans averaging 8.8 months post-treatment.

### Image 6

Sustained rehabilitative outcomes are observed in longitudinal, follow-up scans averaging 8.8 months post-treatment. All SIS scores within the denoted range (area shaded green) are considered within normal limits.
3. DISCUSSION & CONCLUSION

We present practice-based evidence for the standardized application of fNCI, which is currently used in directing neurorehabilitation, with particular efficiency in mTBI. We indicate the clinical appropriateness of this image-guided approach through iterative pilot testing, standardized administration, and individualized, normative-based contextualization. We further demonstrate the rehabilitative guidance capability of fNCI in establishing EPIC treatment standards that prioritize neurovascularly-uncoupled regions of interest unique to each patient, and support the targeted, multi-method, cyclical, and sustained approach employed by our multidisciplinary team.

Positive patient outcomes—graphically represented using conventional and fNCI-directed measures—advocate fNCI’s efficacy in the accelerated and longitudinal neurorehabilitation of mTBI across a variety of concussion profiles.

Longitudinal data collection has observed a maintained SIS score within normal limits, signifying the probable restoration of pre-traumatic NVC and re-establishment of default NVC efficiency. Continued longitudinal data collection will likely explain the mechanistic observation of these positive outcomes.

Though our positive treatment outcomes support the role of NVC in PCS, the complex interconnectedness of vast neural correlate systems found within the brain advocate the etiological potential of multiple mechanical failings (e.g. neuronal dysfunction, signaling/timing disruptions, and/or neurotransmitter dysregulation).

Therefore, we support continual exploration of other advanced neurorehabilitative therapies and their relationships to persistent models of mTBI.

However, standardized application of this evidence-based practice in general neurocognitive assessment and rehabilitation may be key to establishing clinical fMRI practice standards specifically in guiding neurorehabilitative outcomes.
SUPPORTING PUBLICATIONS


REFERENCES


