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# Reversing Brain Damage in Former NFL Players: Implications for Traumatic Brain Injury and Substance Abuse Rehabilitation†

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**Abstract**—Brain injuries are common in professional American football players. Finding effective rehabilitation strategies can have widespread implications not only for retired players but also for patients with traumatic brain injury and substance abuse. An open label pragmatic clinical intervention was conducted in an outpatient neuropsychiatric clinic with 30 retired NFL players who demonstrated brain damage and cognitive impairment. The study included weight loss (if appropriate); fish oil (5.6 grams a day); a high-potency multiple vitamin; and a formulated brain enhancement supplement that included nutrients to enhance blood flow (ginkgo and vinpocetine), acetylcholine (acetyl-l-carnitine and huperzine A), and antioxidant activity (alpha-lipoic acid and n-acetyl-cysteine). The trial average was six months. Outcome measures were Microcog Assessment of Cognitive Functioning and brain SPECT imaging. In the retest situation, corrected for practice effect, there were statistically significant increases in scores of attention, memory, reasoning, information processing speed and accuracy on the Microcog. The brain SPECT scans, as a group, showed increased brain perfusion, especially in the prefrontal cortex, parietal lobes, occipital lobes, anterior cingulate gyrus and cerebellum. This study demonstrates that cognitive and cerebral blood flow improvements are possible in this group with multiple interventions.

**Keywords**—brain trauma, football, MicroCog, rehabilitation, SPECT

Brain injuries are common in professional American football players, and their incidence has been associated with mild cognitive impairment, dementia and depression (Guskiewicz et al. 2007, 2005). A study sponsored by the National Football League (NFL) found that retired players aged 30 to 49 receive a dementia-related diagnosis at a rate of 1.9%, or 20 times the rate of age-matched populations, while 6.1% of players over the age of 50 receive a dementia-related diagnosis representing five times the national average of 1.2% (Weir, Jackson & Sonnega 2009). In a recent study conducted on 100 active and retired NFL players the authors found overall decreased cerebral perfusion and a higher incidence of depression, obesity and memory and attentional problems compared to the general population (Amen et al. 2011). In addition, brain injuries have also been found to

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**TABLE 1**
**Before and After Percentile Scores on the Microcog Assessment of Cognitive Functioning in 30 NFL Players**

| MicroCog Domains | Before Mean (Std. Dev) | After Mean (Std. Dev) | *p* Value | Number of Players with > 50% improvement |
|---|---|---|---|---|
| General Cognitive Functioning | 31.8 (24.1) | 43.4 (25.7) | <0.000 | 14 |
| General Cognitive Proficiency | 24.7 (20.1) | 35.2 (23.5) | <0.000 | 14 |
| Processing Speed | 33.1 (24.8) | 39.3 (25.5) | 0.026 | 12 |
| Processing Accuracy | 40.9 (28.7) | 48.5 (29.1) | 0.012 | 13 |
| Attention | 38.4 (26.2) | 48.7 (27.6) | 0.025 | 9 |
| Reasoning | 32.7 (25.7) | 41.6 (28.0) | 0.006 | 11 |
| Memory | 33.8 (27.4) | 42.9 (28.4) | 0.022 | 17 |
| Spatial Processing | 69.0 (21.8) | 74.3 (13.2) | 0.154 | 3 |
| Reaction Time | 70.2 (24.5) | 74.67 (22.9) | 0.669 | 6 |

increase the risk of substance abuse (Olson-Madden et al. 2010; Graham & Caron 2008).

Brain injuries affect not only retired professional football players, but also an estimated 1.7 million people annually (CDC 2010) and many soldiers returning from Iraq and Afghanistan. In addition, substance abusers also experience high levels of brain damage from the toxic effects of the drugs or alcohol and the higher incidence of brain injuries during intoxication (Gold et al. 2009).

Evaluating potential treatments to rehabilitate or reverse brain damage is important in many clinical populations, especially for patients with traumatic brain injury and substance abuse. Brain SPECT imaging is a standard, widely available functional brain imaging tool that has been found to help evaluate baseline brain function and the effect of treatment interventions (Amen 2010). In this report we describe our experience with 30 retired NFL players who took part in a pragmatic open-label, clinical intervention to attempt to reverse brain damage and cognitive dysfunction.

## MATERIALS AND METHODS

### Recruitment

As part of a larger study we recruited 100 retired NFL players, representing 27 teams and all positions. Each player met our inclusion criteria of being on an active NFL roster for a minimum of three years. We excluded any subjects who could not cease taking psychoactive medications (recreational or otherwise) for an appropriate washout period prior to scanning. All subjects signed informed consent as part of an IRB protocol. The study started in 2009 and concluded in 2010.

### Evaluation Procedures

Each participant was interviewed by a physician and completed a detailed medical and psychiatric history. Weight, height and waist size were obtained on all participants and body mass index (BMI) and waist-to-height ratios were calculated. As part of the evaluation each participant took the Microcog Assessment of Cognitive Functioning (MACF; Powell et al. 2004), which contains nine subtests: general cognitive functioning, general cognitive proficiency, information processing speed, information processing accuracy, attention, reasoning, memory, spatial processing and reaction time. The MACF scores were compared to its own standardized sample (n= 810) chosen to be representative of the U.S. population of adults between the ages of 18 and 89 in regards to education, gender, and ethnicity. The MACF was chosen because the means from test to retest were stable over time and showed little practice effect (Powell et al. 1993).

In addition, each subject underwent high-resolution brain SPECT imaging to measure regional cerebral blood flow (rCBF). Each subject received an age/weight-appropriate dose of Tc99m HMPAO intravenously. Subjects were injected in normal lighting while they performed a go, no-go, continuous performance task. The radiopharmaceutical was injected three minutes after starting the 15-minute test. All subjects completed the task. Subjects were then scanned 30 minutes later using a high-resolution Picker Prism 3000 triple-headed gamma camera with fan beam collimators, acquiring data in 128x128 matrices, yielding 120 images per scan with each image separated by 3 degrees spanning 360 degrees.

SPECT data was processed and attenuation correction performed using general linear (Chang) methods. All images were reconstructed and resliced using an oblique reformatting program, according to anterior-posterior commissure line so final images were similarly aligned for analysis.

### Intervention

All subjects were offered the opportunity to participate in a pragmatic interventional phase. Pragmatic interventions are ones that participants might experience in a "real-world" clinical situation. The interventions included education on a brain-healthy lifestyle, such as proper nutrition, regular exercise, limiting alcohol, eliminating drug abuse and cigarette smoking, getting appropriate sleep, and having sleep apnea assessed if symptoms were endorsed. As obesity has been associated with dementia and a smaller brain (Raji et al. 2010),

**TABLE 2**
**Significant Areas of Increased Perfusion After Treatment at $p < 0.001$**

| AAL Areas | Cluster Size | Location | | | Z |
|---|---|---|---|---|---|
| Prefrontal Infer-Mid-Sup Lt | 473 | -24 | 62 | 16 | 4.69 |
| Prefrontal Mid Sup Rt | 2064 | 36 | 50 | 24 | 3.58 |
| Inferior Orbital Lt | 244 | -2 | 52 | -32 | 4.05 |
| Anterior Cingulate Rt | 79 | 12 | 40 | 24 | 3.68 |
| Parietal/Angular Lt | 77 | -60 | -54 | 48 | 4.49 |
| Parietal/Precuneus Lt | 205 | -12 | -56 | 74 | 4.32 |
| Parietal/Precuneus Rt | 188 | 20 | -54 | 78 | 4.35 |
| Occipital/Cuneus Lt | 136 | 2 | -102 | 18 | 4.30 |
| Occipital/Cuneus Rt | 197 | 26 | -104 | 8 | 3.89 |
| Cerebellum Crus Rt | 104 | 48 | -78 | -22 | 4.01 |

we encouraged overweight or obese players to lose weight. Forty-eight percent of players in the initial study were overweight or obese, even taking into account their large body frames. Author KW ran an optional weight-loss group for players. In addition, players were given 5.6 grams of fish oil a day, containing 1720mg of EPA and 1160mg of DHA, as omega-three fatty acid supplementation has shown benefits with memory, mood and cognition (Michael-Titus 2009; Conklin et al. 2007) and a high-potency multiple vitamin, which has been shown to enhance mental performance (Kennedy et al. 2010). Participants in the interventional study also received a brain enhancement supplement that contained clinically effective dosages of nutrients to enhance blood flow: ginkgo (Santos et al. 2003) and vinpocetine (Gulyás et al. 2002); decrease cortisol: phosphatidylserine (Monteleone et al. 1990); enhance acetylcholine: acetyl-l-carnitine (Jones, McDonald & Borum 2010) and huperzine A (Zhang, Yan & Tang 2008); and enhance antioxidants: alpha-lipoic acid (Arguelles et al. 2010) and n-acetyl-cysteine (Dodd et al. 2008). The trial for each participant ranged from two to 12 months, with the average being six months, depending on the participant's ability to travel to the study location in Southern California.

In the follow-up evaluation, participants underwent a clinical interview, completed a questionnaire on their progress, had a follow-up brain SPECT scan, and retook the MACF.

### SPECT Image Analysis

Differences in HMPAO uptake were analyzed using SPM8 software (Wellcome Department of Cognitive Neurology, London, UK) implemented on the Matlab platform (MathWorks Inc., Sherborn, MA). Statistical parametric maps (SPMs) are spatially extended statistical processes that are constructed to test hypotheses about regionally specific effects in neuroimaging data. Statistical parametric mapping combines the general linear model and the theory of Gaussian random fields to make statistical inferences about regional effects (Friston, Holmes & Worsley 1995). The images were spatially normalized using a twelve parameter affine transformation followed by nonlinear deformations (Ashburner & Friston 1999) to minimizing the residual sum of squares between each scan and a reference or template image conforming to the standard space defined by the Montreal Neurological Institute (MNI) template. The original image matrix obtained at 128x128x29 with voxel sizes of 2.16mm x 2.16mm x 6.48mm were transformed and resliced to a 79x95x68 matrix with voxel sizes of 2mm x 2mm x 2mm consistent with the MNI template. Images were smoothed using an 8mm FWHM isotropic Gaussian kernel.

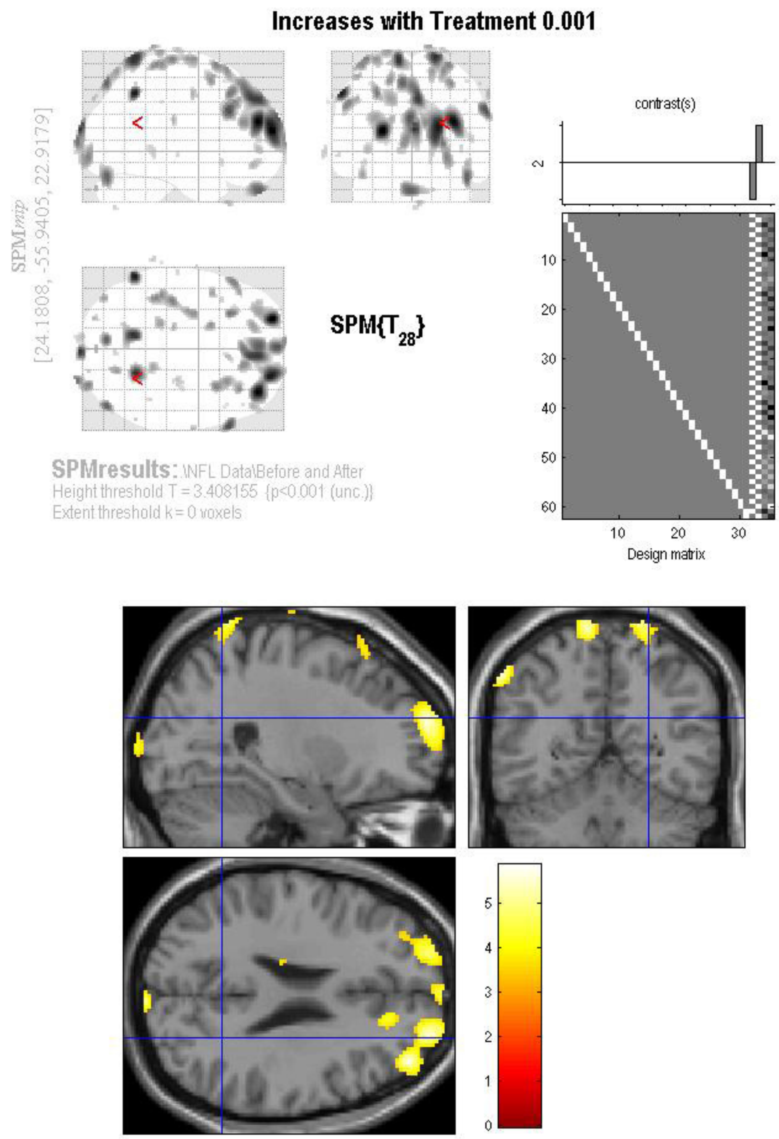
As a group, we compared participants' original SPECT scans with their follow-up scans using a paired t-test with ANCOVA. Based on our prior study (Amen et al. 2011), our hypothesis was that we would see increased rCBF in the prefrontal cortex, anterior cingulate gyrus, temporal lobes, parietal lobes, occipital lobes and cerebellum. SPM(z) score differences for a-priori regions of interest (Table 2) were computed using the WFU PickAtlas toolbox within the SPM8 framework (Maldjian et al. 2003, Maldjian, Laurienti & Burdette 2004).

## RESULTS

In the retest situation, corrected for practice effect, there were statistically significant increases in MACF scores in general cognitive functioning, general cognitive proficiency, attention, memory, reasoning, information processing speed and accuracy (see Table 1). There were also increases in spatial processing and reaction time, although these were not statistically significant. Many of the participants had robust increases in performance. Table 1 also lists the number of participants in each category who had greater than a 50% increase in percentile scores.

The brain SPECT scans also showed significant increases in brain perfusion at $p < 0.001$, especially in the prefrontal cortex, anterior cingulate gyrus, parietal lobes, occipital lobes, and cerebellum (see Table 2 for specific areas of significant increases and Figure 1 for a visual representation of the areas of significant increase). No significant

**FIGURE 1**
**Areas of Increased Perfusion on SPECT with Treatment at $p < 0.001$ are Highlighted**




decreases were seen. These findings were consistent with our hypothesis, except at this level we did not see increases in temporal lobe perfusion. When the threshold was lowered to $p < 0.05$ there were significant increases in the left and right fusiform gyrus and lateral temporal lobes. Symptomatically, participants reported increases in memory (69%), attention (53%), mood (38%), motivation (38%), and sleep (25%).

## CONCLUSIONS

This clinical study targeted retired professional football players who had experienced traumatic brain injuries as a result of numerous impacts over extended periods of time. Our goal was to design an interventional strategy that would improve cognitive function by enhancing cerebral blood flow, acetylcholine and antioxidant activity. We utilized a standard brain imaging tool (SPECT) and a standard computerized neuropsychological test (MACF) to determine if improvement could be obtained. Our findings on this unique population are encouraging as we observed significant improvements in general cognitive functioning, information processing speed, attention and memory in close to half of the participants. Plus, there were significant increases in regional cerebral blood flow seen on SPECT.

The implications of this study directly apply to the larger traumatic brain injury and substance abuse communities. We were able to demonstrate improvement in brain function and cognitive performance in retired players who sustained brain injuries often decades previously, demonstrating brain plasticity. This is an area where much more research is needed. Because of the high incidence of traumatic brain injury and the long-term damaging effects of substance abuse, focusing on brain health and brain rehabilitation strategies in addiction treatment programs could potentially significantly improve patient outcomes.

This clinical study is limited by its nonrandomized, open-label, multifaceted design and the results must be interpreted with caution. Our hope is to use this trial as a starting point to more rigorously study the individual parts of the treatment protocol and to extend the study to include other types of brain damage, including blast injuries, single-incident brain traumas, and substance abuse.

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