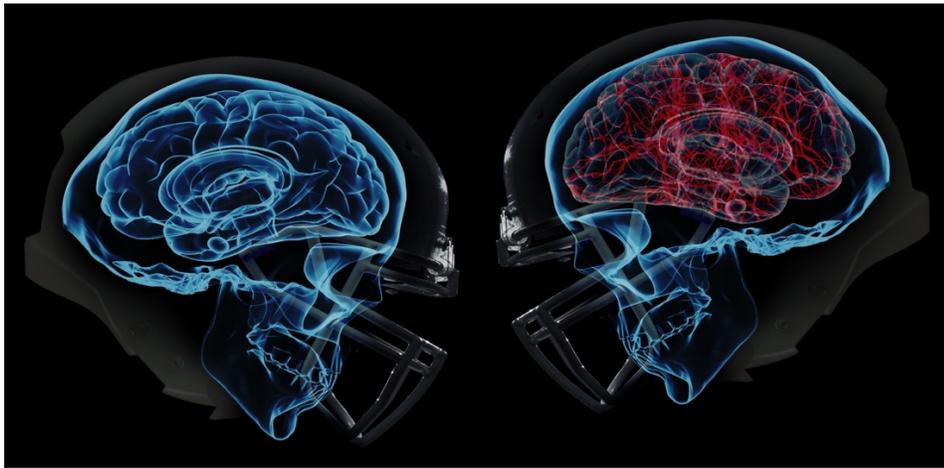


NEUROFEEDBACK INNOVATIONS FOR CONCUSSION WITH RETIRED NFL PLAYERS



4/1/17

Evaluating the Effectiveness of Ultra Low Power Pulsed Electric Current EEG Biofeedback in Treating Symptoms of Repeated Traumatic Brain Injury and Neurocognitive disorder with Retired NFL players

ABSTRACT

Between October 2015 and November 2016, 9 clinical sites assessed over 80 former NFL players with a history of repeated traumatic brain injury (rTBI) and neurocognitive disorder. 13 of these players completed a standardized protocol of a unique form of Neurofeedback treatment using a single, specific instrument commonly referred to as Direct Neurofeedback. All participants had played at least 4 years in the NFL, had a minimum diagnosis of mild-neurocognitive disorder and were not involved in any other treatment interventions during the study. Building off a previously successful pilot study with this technology and population, a more robust, standardized training protocol was developed together with advanced assessment and measurement techniques for pre, mid and post treatment measures.

The objective of this study was to decrease symptoms related to rTBI and show memory, physiological and mood improvements. Statistically significant results occurred in all testing measures, including Brain imaging, suggesting that this form of Neurofeedback is a viable and repeatable treatment approach.

Neurofeedback Innovations for Concussion with Retired NFL Players

EVALUATING THE EFFECTIVENESS OF ULTRA LOW POWER PULSED ELECTRIC CURRENT EEG BIOFEEDBACK IN TREATING SYMPTOMS OF REPEATED TRAUMATIC BRAIN INJURY AND NEUROCOGNITIVE DISORDER WITH RETIRED NFL PLAYERS

The following is a summary of data presented at the 2017 annual AAPB conference in Chicago, IL on March 17, 2017. This is not the final publication, which is currently being prepared for peer-review and journal publication. This data is not intended for public circulation.

BACKGROUND

The long-term consequences of repetitive head impacts have been described since the early 20th century. While Concussion and Post-Concussion Syndrome are shown to be temporary states; research suggests that repetitive traumatic brain injuries (rTBI) are likely to contribute to the onset of Mild or Major Cognitive Disorder (previously referred to as Dementia), and/or Chronic Traumatic Encephalopathy (CTE) years or even decades after the recovery of acute effects of head injury. For decades, various forms of Neurofeedback have been used to improve symptoms from Post-Concussion Syndrome. Over 25 peer-reviewed studies involving over 600 subjects using various Neurofeedback techniques and protocols have been shown to remediate symptoms and improve brain function in individuals with acute or long-term effects of Traumatic Brain Injury (TBI).

In 2014, pilot data on the effectiveness of ultra-low power pulsed electric current Biofeedback (Direct Neurofeedback) to remediate symptoms of repetitive traumatic brain injury in 9 retired NFL athletes was presented at an international neuroscience conference. The results this study after 20 total sessions (approximately 10 weeks) showed statistically significant improvements in symptom reduction and functional brain imaging (qEEG) normalization. This pilot data spurred the collaborative effort to further the research & attain higher quality measurements to understand the true impact of the intervention.

OBJECTIVE

The objective of this study was to determine the short-term and long-term efficacy of this Neurofeedback approach in the reduction of symptoms related to rTBI and enhancement of neurocognitive function. Using advanced functional imaging, brain performance testing and multiple symptom measurements, we hypothesized the intervention would produce symptom reduction, brain performance improvement and positive changes in brain imaging over the course of 24 sessions of standardized protocol treatment.

METHOD

Equipment: Ultra-Low Pulsed Electric Current EEG Biofeedback

The study device was the J&J I-330 C2+2-Channel EEG Amplifier, running a modified version of PhysioLab USE3 software. The device is registered with the FDA under a 510(k) exemption. This equipment has been sold under the various trade names, Clarity Direct Neurofeedback, Neurogen, HPN and Iasis Microcurrent Neurofeedback. Treatment using this equipment is commonly referred to as Direct Neurofeedback.

Direct Neurofeedback is a unique treatment that allows the brain to “get out of” frozen, stuck patterns. In *Direct Neurofeedback* clients generally notice changes either immediately or within the first few sessions. Immediate results, fewer and shorter duration of sessions together with the ease and simplicity of treatment distinguish *Direct Neurofeedback* from traditional neurofeedback.

In all Neurofeedback, sensors are placed on the scalp. These sensors measure electrical activity of the brain and generate an EEG (electroencephalogram) just like the electrical activity of the heart generates an EKG (electrocardiogram). With Direct Neurofeedback, once feedback begins, a very weak, imperceptible signal is sent back to the brain. This signal causes a tiny fluctuation in brainwave patterns and allows the brain to “get out of” frozen, stuck patterns. It’s like rebooting a frozen computer. *Direct Neurofeedback* “dis-entrains” the brain from unhealthy stuck pathways. Patients don’t do anything other than sit still for a few moments. That brief, tiny signal to the brain does all the work.

Direct Neurofeedback is a positive feedback loop. The electrical activity from the brain determines what signal goes back to the brain. This signal causes a change in the brainwaves. This change in brainwaves then causes a change in the signal going back to the brain. Overtime, the brain gets stronger and more resilient and longer stimulation is required to elicit the desired effect. At a certain point, the brain has found homeostasis and regular training is no longer needed. It is our hypothesis that continued maintenance of 2 sessions per year would be beneficial to keep the brain in homeostasis.

Subjects: Former NFL Players

Over 80 former NFL players were assessed. For various reasons including time commitment, inaccessibility, concerns about the NFL concussion lawsuit and strict inclusion criteria, only 24 players started treatment. 13 players completed all treatment sessions and assessments.

Inclusion Criteria:

- Played in the NFL for at least 4 years
- At least one diagnosed concussion during play
- Minimum diagnosis of mild-neurocognitive disorder
- Completed pre, mid and post assessments
- Completed 24 sessions of treatment at 2 sessions per week
- No other form of treatment or cognitive improvement to be used between pre & post assessment

Assessment Measures:

CNSVS: Central Nervous System Vital Signs

Peer-reviewed and reliable Neurocognitive testing using a battery of computer administered tests to derive 12 domain scores including: Neurocognitive Index, Composite Memory, Verbal Memory, Visual Memory, Psychomotor Speed, Reaction Time, Complex Attention, Cognitive Flexibility, Processing Speed, Executive Function, Simple Attention and Motor Speed.

Self-Report Symptoms Scales and Questionnaires

- Medical Outcomes Survey (MOS) - Quality of life
- Patient Health Questionnaire (PHQ-9) - Measurement of depression
- Memory Questionnaire (MEMQ) - Measurement of memory and concentration
- Head Injury Questionnaire (HIQ) - Head injury common symptoms
- Neurobehavioral Symptom Inventory (NSI) - Typical post-concussive symptoms
- Rivermead Post-Concussion Symptoms Questionnaire - A commonly used “side-line” questionnaire for concussion
- Symptom severity (0-10) tracking across 16 different domains each session.

Functional Brain Imaging - qEEG (Quantitative Electroencephalogram)

Medical grade equipment was used to record digitized EEG signals from 19-channels across the scalp using the 10-20 international classification system. An analysis of edited raw data against the Thatcher Life Span Reference Data Base, (Thatcher et al, Science, Vol. 236: 1110-1113, 1987), matched for age, gender, and handedness was performed on individual pretest and posttest QEEGs to assess functional integrity of cortico-cortical neural function, and to determine direction of change before doing a group analysis. Data base comparisons were conducted on measures of coherence, phase, amplitude asymmetry, and relative power.

Treatment:

Protocol:

A progressive protocol was used to systematically increase from a 2-site placement for a total of 1 minute of stimulation, towards whole-brain stimulation for 6.5 minutes total.

GROUP RESULTS

Full Brain Imaging (qEEG) Analysis and findings found in Appendix I.

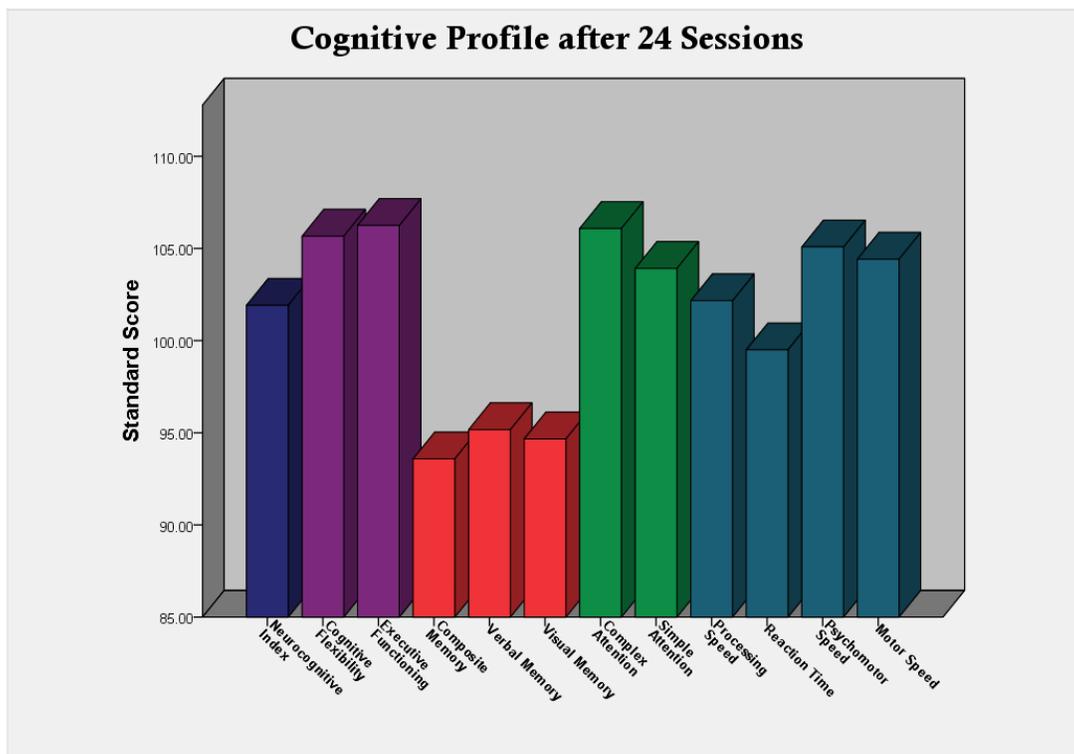
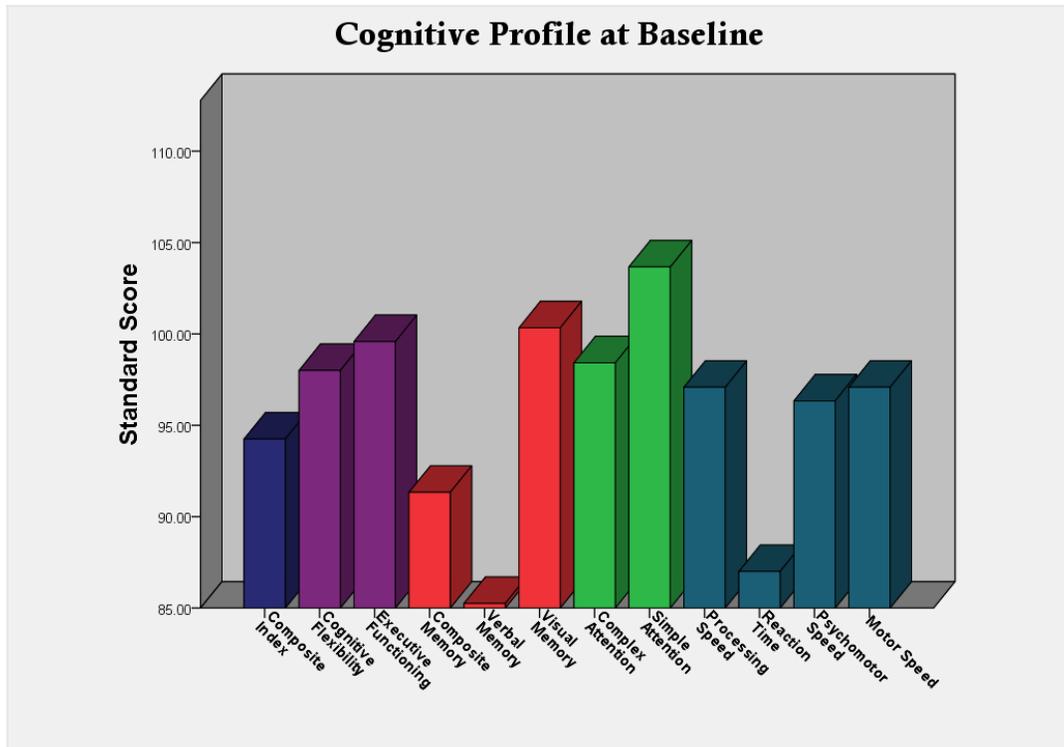
Highly significant ($p \leq .01$) changes:

- CNSVS - Neurocognitive Index performance
- Symptom Report - Sleep, Irritability, Anxiety, Frustration, Mood, Depression, Brain Fog
- Rivermead total score, plus Somatosensory and Affective Domains
- MOS Questionnaire - Perceived Health Change and Emotional Well-Being
- PHQ-9 depression rating total score
- Brain Imaging (qEEG) - Posterior High Gamma (40-50Hz) reduction

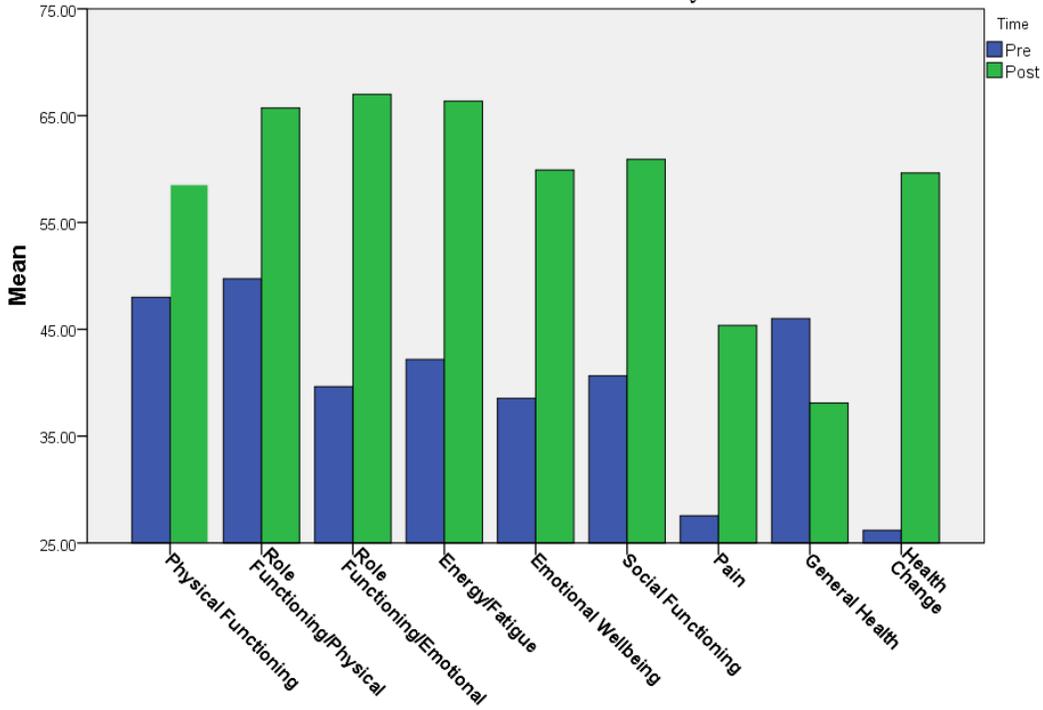
Significant ($p \leq .05$) changes:

- CNSVS - Cognitive Flexibility, Verbal Memory, Reaction Time, Psychomotor Speed
- Symptom Report - Headaches, Fatigue, Light Sensitivity, Aggression, Memory, Concentration
- Questionnaires - Total Scores of NSI, MEMQ and HIQ
- Brain Imaging (qEEG) - Each individual record showed significant improvement between pretest and posttest. Group reductions in Delta & Theta absolute power. Coherence normalization in all frequencies.

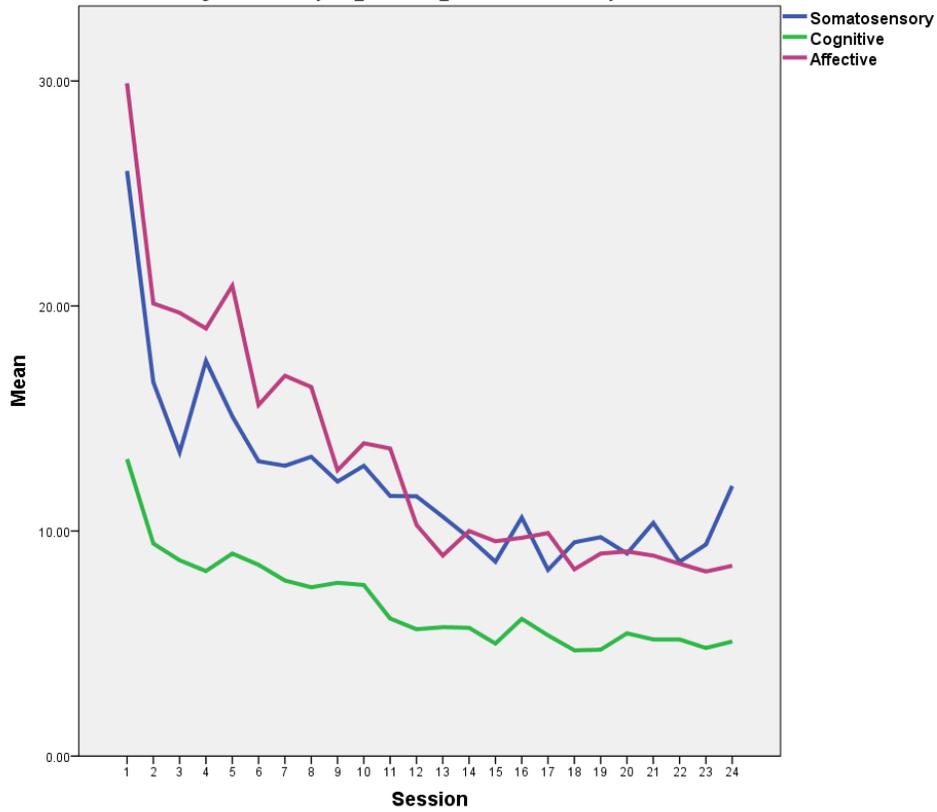
Sample charts showing change from Pre - Post treatment:



Medical Outcomes Survey



Subjective Symptoms per Session by Factor



SINGLE CASE STUDY

Joe DeLamielleure

Joe played for 13 years in the NFL and never missed a game or practice. His overall physical health was ideal prior to participation in the study. Nutrition, exercise, family support, life goals and aspirations, metabolic and hormonal balance were all well maintained and in the best condition possible. Joe and his family's main complaints were surrounding poor sleep, attention, memory, irritability and general cognitive decline. Joe's cognitive capabilities and behavior started improving in early treatment sessions and continued throughout the treatment process. A significant improvement in sleep was a key-factor influencing other cognitive and behavioral changes. As assessed by Joe, his symptoms improved 75% over the three-month time frame. His wife Gerri estimated an 85% improvement in the same symptoms. Joe's Neurocognitive Index, an overall objective rating of brain performance improved by 25.4%, and his brain imaging QEEG significantly improved to within normal limits.

"After never missing a game or practice in my 13 year professional NFL career, you can imagine I took a few hits to the head. A few years after my induction into the Pro Football Hall of Fame my family and I started noticing increasing symptoms related to attention span, irritability, sleep disturbances, comprehension, memory, anxiety and more. I tried everything I could get my hands on, experimental or not. After three-month's of Neurofeedback, I was able to sleep through the entire night, my anxiety and irritability have disappeared, my attention and comprehension have significantly improved and my memory is better than it has been in decades! One year after treatment, with no further interventions, I feel even better and my family and friends recognize the same (if not more) changes."

- Joe DeLamielleure

One year post-testing, with no additional treatment intervention, revealed a further decrease in symptoms with Joe estimating a 92% improvement from pre-treatment and his wife Gerri estimating a 93% improvement. Joe's Neurocognitive Index has improved further, now at a 33.8% improvement from pre-treatment results.



CNSVS Results:

CNS Vital Signs Report		Test Date: October 26, 2015 10:00:36	
Subject Reference/ID: 107680		Administrator: Seth Conger	
Age: 64		Language: English (United States)	
Total Test Time: 58:34 (min:secs)		Online Version 1.0	

Patient Profile	Percentile Range				> 74	25 - 74	9 - 24	2 - 8	< 2
	Standard Score Range				> 109	90 - 109	80 - 89	70 - 79	< 70
Domain Scores	Subject Score	Standard Score	Percentile	Valid Score**	Above	Average	Low Average	Low	Very Low
Neurocognitive Index (NCI)	NA	71	3	Yes				X	
Composite Memory	75	65	1	Yes					X
Verbal Memory	37	60	1	Yes					X
Visual Memory	38	81	10	Yes			X		
Psychomotor Speed	114	75	5	Yes				X	
Reaction Time*	950	72	3	Yes				X	
Complex Attention*	23	77	6	Yes				X	
Cognitive Flexibility	-2	66	1	Yes					X
Processing Speed	43	99	47	Yes		X			
Executive Function	4	69	2	Yes					X
Simple Attention	40	108	70	Yes		X			
Motor Speed	71	67	1	Yes					X

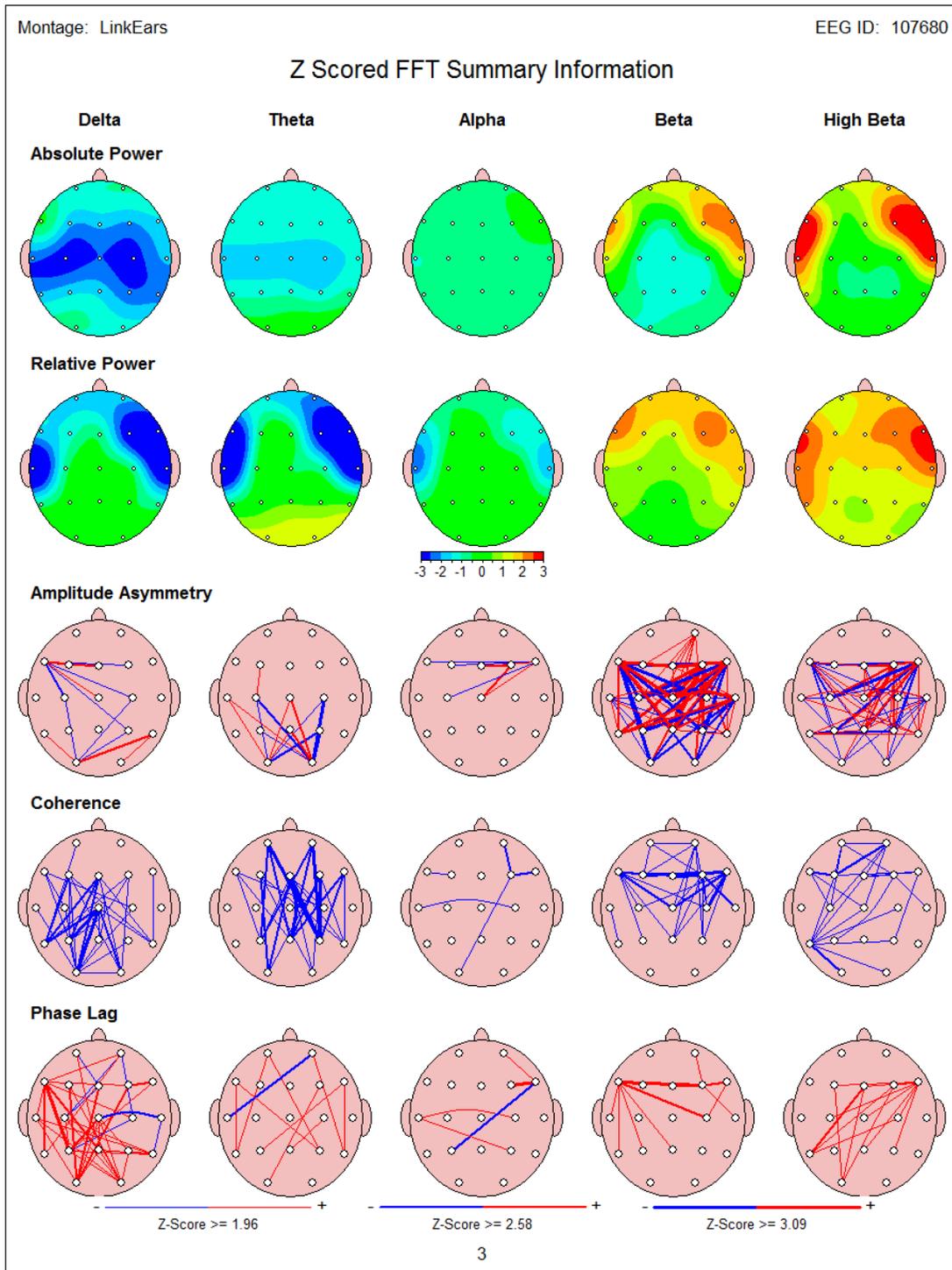
CNS Vital Signs Report		Test Date: January 25, 2016 09:14:32	
Subject Reference/ID: CLT08		Administrator: Seth Conger	
Age: 64		Language: English (United States)	
Total Test Time: 47:23 (min:secs)		Online Version 1.0	

Patient Profile	Percentile Range				> 74	25 - 74	9 - 24	2 - 8	< 2
	Standard Score Range				> 109	90 - 109	80 - 89	70 - 79	< 70
Domain Scores	Subject Score	Standard Score	Percentile	Valid Score**	Above	Average	Low Average	Low	Very Low
Neurocognitive Index (NCI)	NA	89	23	Yes			X		
Composite Memory	86	85	16	Yes			X		
Verbal Memory	52	106	66	Yes		X			
Visual Memory	34	70	2	Yes				X	
Psychomotor Speed	134	88	21	Yes			X		
Reaction Time*	888	79	8	Yes				X	
Complex Attention*	8	105	63	Yes		X			
Cognitive Flexibility	25	90	25	Yes		X			
Processing Speed	37	91	27	Yes		X			
Executive Function	25	88	21	Yes			X		
Simple Attention	40	108	70	Yes		X			
Motor Speed	93	87	19	Yes			X		

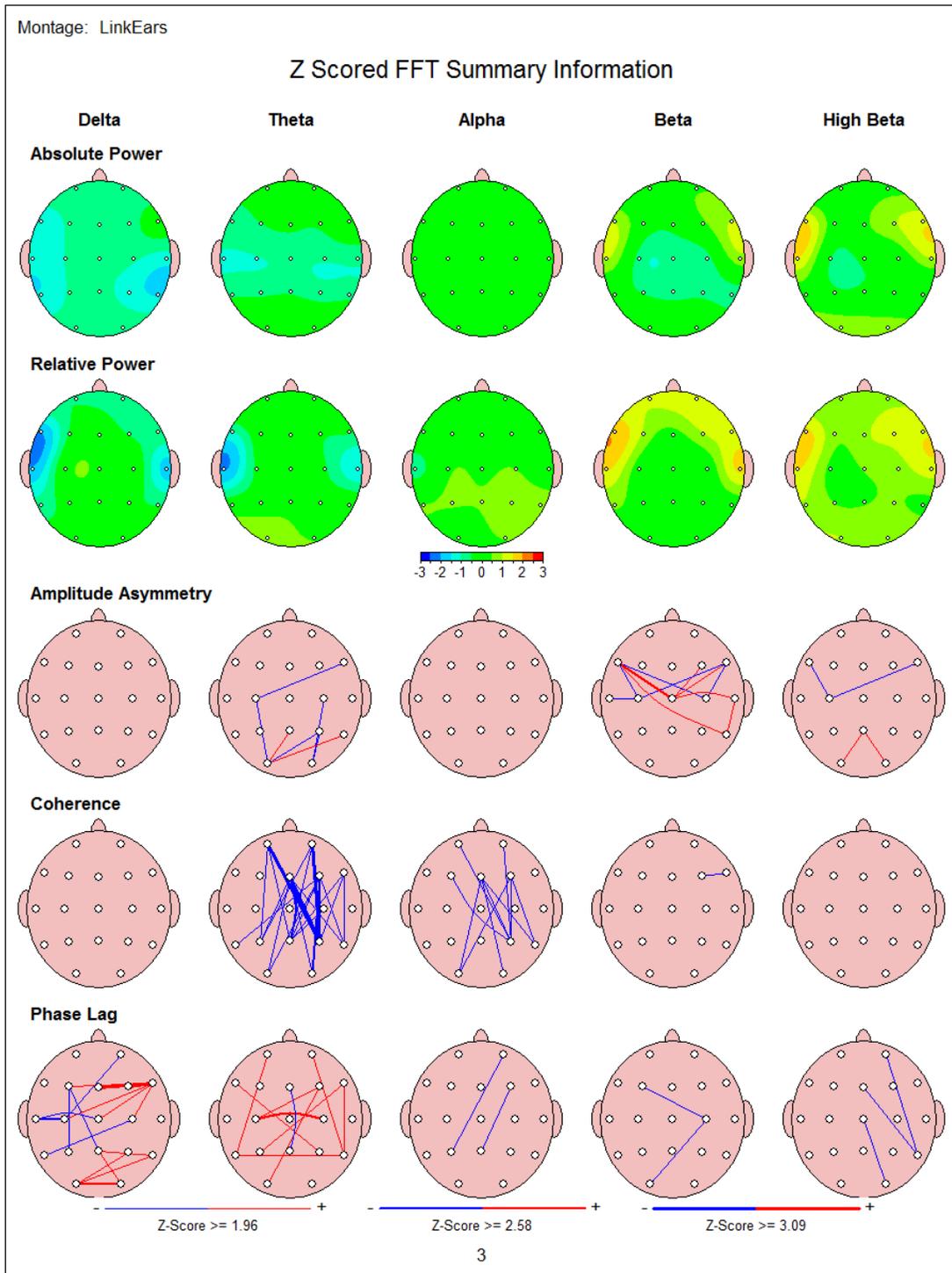
CNS Vital Signs Report		Test Date: February 20, 2017 09:58:15	
Patient ID: 107680		Administrator: administrator	
Age: 65		Language: English (United States)	
Total Test Time: 45:09 (min:secs)	CNSVS Duration: 34:40 (min:secs)	Version 4.0.82	

Patient Profile:	Percentile Range				> 74	25 - 74	9 - 24	2 - 8	< 2
	Standard Score Range				> 109	90 - 109	80 - 89	70 - 79	< 70
Domain Scores	Patient Score	Standard Score	Percentile	VI**	Above	Average	Low Average	Low	Very Low
Neurocognition Index (NCI)		95	37	Yes		x			
Composite Memory	81	76	5	Yes				x	
Verbal Memory	45	84	14	Yes			x		
Visual Memory	36	75	5	Yes				x	
Psychomotor Speed	141	93	32	Yes		x			
Reaction Time*	884	79	8	Yes				x	
Complex Attention*	2	117	87	Yes	x				
Cognitive Flexibility	46	108	70	Yes		x			
Processing Speed	40	95	37	Yes		x			
Executive Function	47	108	70	Yes		x			
Simple Attention	40	108	70	Yes		x			
Motor Speed	99	92	30	Yes		x			

qEEG Functional Brain Imaging: Pre-Treatment Eyes Open Image



qEEG Functional Brain Imaging: Post-Treatment Eyes Open Image



CONCLUSION

This pilot study provides evidence that this form of Ultra Low Power Pulsed Electric Current EEG Biofeedback can be a viable treatment approach for neurocognitive symptoms from rTBI. It is not clear if the treatment has any effect on the aggregation of tau protein in the brain, the signature of CTE; until reliable biomarkers of CTE in a living brain are readily available this question will remain.

Although these results are encouraging and showed improvement over a past pilot study, a larger sample size and control group population is needed. The next objective will be to identify funding for a larger collaborative effort to study this and other viable forms of treatment for rTBI, concussions and resulting cognitive disorder(s) in multiple populations.

Clinical Trial Sites:

Carolina HealthSpan Institute - Charlotte, NC
SonoMarin Neurofeedback - Sonoma, CA
Palo-Alto Neurofeedback - Palo Alto, CA
New Hope for the Brain - Denver, CO
Midwest Neurofeedback - Kansas City, KS
Linden Attention Learning Center - Laguna Hills, CA
NeuroQuest - Chicago, IL
Brain Wellness and Biofeedback Center - Washington DC
Brain Strength Training - New York, NY
MindSpa Integrative Wellness Center - Sarasota, FL
The Dubin Clinic - Los Angeles, CA

Clinical Investigators:

Ronald L. Brown, MD | Britney Cirullo, LPC, LCAS, BCN | Seth Conger BCN-T | Alan Strohmayer, PhD, BCN, BCB | Elsa Behr, PhD, BCN | Mary Lee Esty, PhD, BCN, BCB | Eileen Roberts, PhD | Kimberly Bell, MD | Penny Montgomery, PhD, BCN | Glenda Lippmann, PhD | Harry Ford, PhD | Christine Palmquist, EdD, BCN | Laura Bratt, LMLP | George Rozelle, PhD, BCN, QEEG-D | Michael Linden, PhD, BCN | Mark Stern, BCN, BCB | David Dubin, MD

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QEEG ANALYSIS - George Rozelle, PhD, BCN, QEEG-D

PROCEDURE

Eleven subjects at different research locations received QEEG pretests and QEEG posttests. Brain electrical activity was recorded from 19-channels, referenced to linked ears, on high quality amplifiers available at each site, in accordance with the 10-20 International Electrode Placement System.

All data were imported into the Neuroguide QEEG analysis software program. The raw recordings were digitized for data storage and analysis, manually edited to reduce artifact (eye movement, EMG, body movement etc.) and subjected to quantitative spectral analysis. Recording conditions were eyes open (awake and alert) and eyes closed. The raw data were examined in a variety of montages. The results of spectral analysis were displayed in color-coded topographic maps, and statistical reports. The QEEG was based upon at least sixty seconds of edited raw EEG data for each testing condition. For purposes of this study a repeated measures design was used. Paired group t-tests were performed to determine differences attributable to the neurofeedback treatment.

Coherence is a measure of the cross correlation of the amount of shared activity between two scalp regions. High coherence reflects a lack of differentiation, or excess similarity of cortical signal processing in brain subsystems and between regions. Low coherence reflects a lack of connection or increased differentiation of cortical signal processing in brain subsystems and between regions.

Phase is a measure of lead or lag of shared rhythms between regions measured in milliseconds. Phase in a connected system such as the cerebral cortex is a function of: EEG frequency, distance between sites, and conduction velocity. Positive phase lags suggest longer signal processing times than would be expected. Sub cortical systems as well as cortical systems may be involved.

Relative Power shows the distribution of power over the cortex. All frequencies at each recording site should total 100% of power. If there is an increase in percentage power, in one frequency band other frequency bands generally decrease.

Previous clinical trials with NFL subjects revealed very different power and connectivity QEEG findings. This would be expected when considering the types of hits experienced by running backs, defensive backs, and linemen. There is no single signature of TBI. The most common finding was deviations in coherence across all frequency bands. Post testing in the clinical trials indicated coherence was normalized more than power

RESULTS

An analysis of edited raw data against the Thatcher Life Span Reference Data Base, (Thatcher et al, Science, Vol. 236: 1110-1113, 1987), matched for age, gender, and handedness was performed on individual pretest and posttest QEEGs to assess functional integrity of cortico-cortical neural function, and to determine direction of change before doing a group analysis. Data base comparisons were conducted on measures of coherence, phase, amplitude asymmetry, and relative power. Four subjects had elevated hypo coherence, three had hyper coherence, and four had mixed coherence deviations. Nine of eleven individual records showed significant improvement between pretest and posttest. The data were then grouped and analyzed using NeuroBatch and NeuroStat from Applied Neuroscience, Inc.

Pre-post group comparisons of Eyes Closed FFT Absolute Power revealed that 1-7 Hz (delta and theta) and 15-16 Hz were greater at pretest than at posttest. Alpha and low beta 8-14 Hz and beta 17-19 <Hz were higher on posttest. In Figure 1 below, Red indicates pretest greater than posttest and Blue indicates posttest greater than pretest. In Figures 2 and 3, statistically significant differences ($P < 0.05$) were found primarily in delta reduction at the following sites: F4, C4, T4, FZ, CZ, PZ. High gamma (40 – 50 Hz) was reduced at the $P < 0.01$ level in posterior sites. Significant coherence differences (Figures 4 and 5) were evident in all frequency bands. Coherence moved toward normalization in nine of eleven cases. Absolute coherence values were used in the group analysis, so significant differences reflect movement toward normalization regardless of initial hypo coherence, hyper coherence, or mixed coherence.

DISCUSSION

As noted earlier TBI can present in different ways in measures of power. In general, one would expect to see increased focal delta and theta, and sometimes increased focal beta and high beta, which may be compensatory or an indication of cortical inflammation. More consistently we see coherence deviations which reflect white matter damage characteristic of TBI. These results show that ultra-low power pulsed electrical feedback can produce significant changes in the QEEG reflecting normalization toward more optimal functioning. These changes can be achieved in 20 – 24 sessions. Follow up studies from previous clinical trials (presented at Association of Applied Psychophysiology and Biofeedback Annual Meeting, Chicago, IL, March 2017) indicated that initial improvements are maintained at three months and, to a lesser degree, at one year, coinciding with continued symptom reduction. Two year follow up studies indicated that without any maintenance treatment, there was a slight regression of QEEG improvements, particularly in coherence measures. This could possibly be due to continued tau protein aggregation in the brain.

Figure 1. FFT Absolute Power Differences mv^2 Pretest – Posttest.

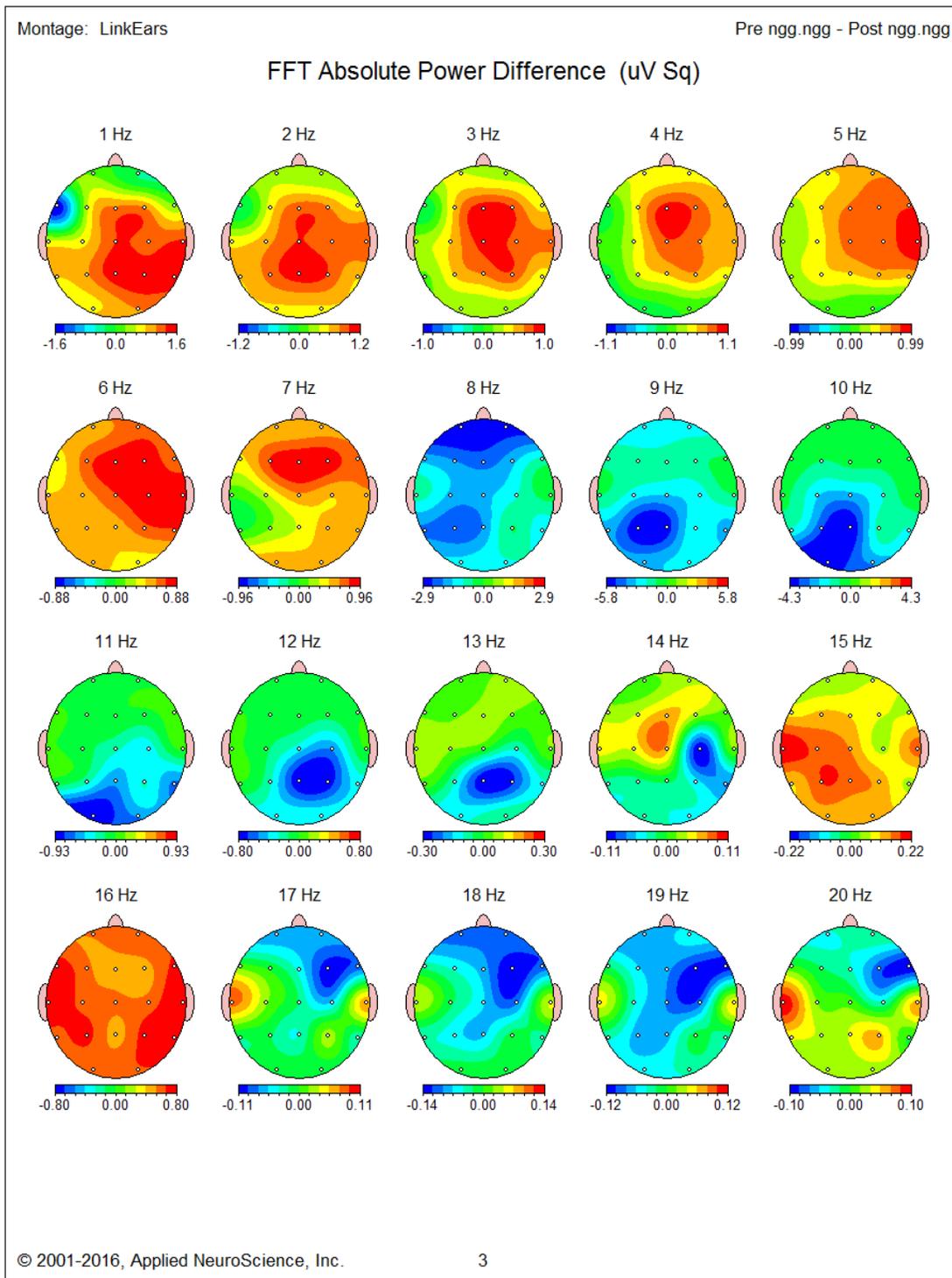


Figure 2. Group Paired T-Test (White indicates $P > 0.06$)

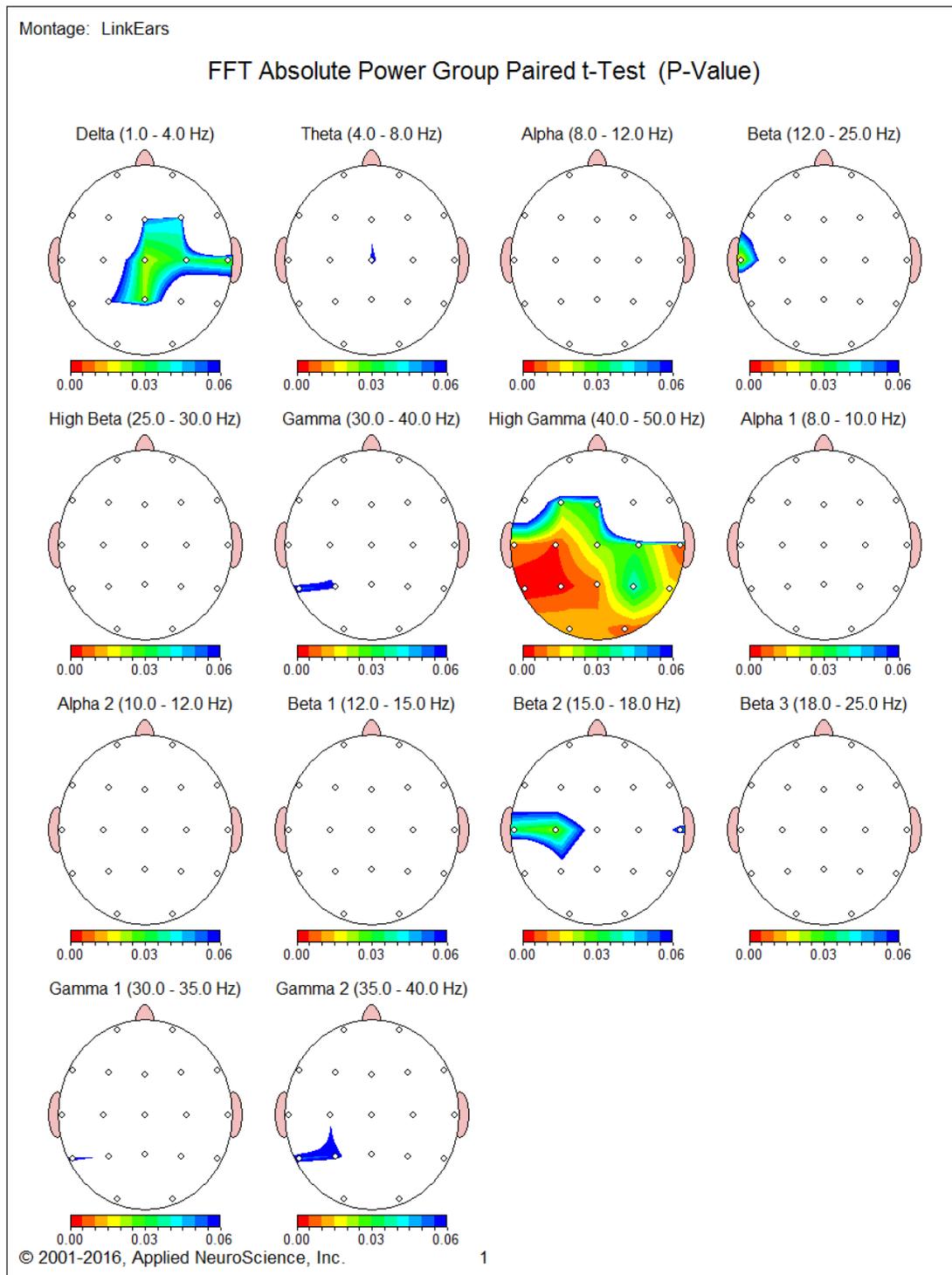


Figure 3. Group Paired T-Test

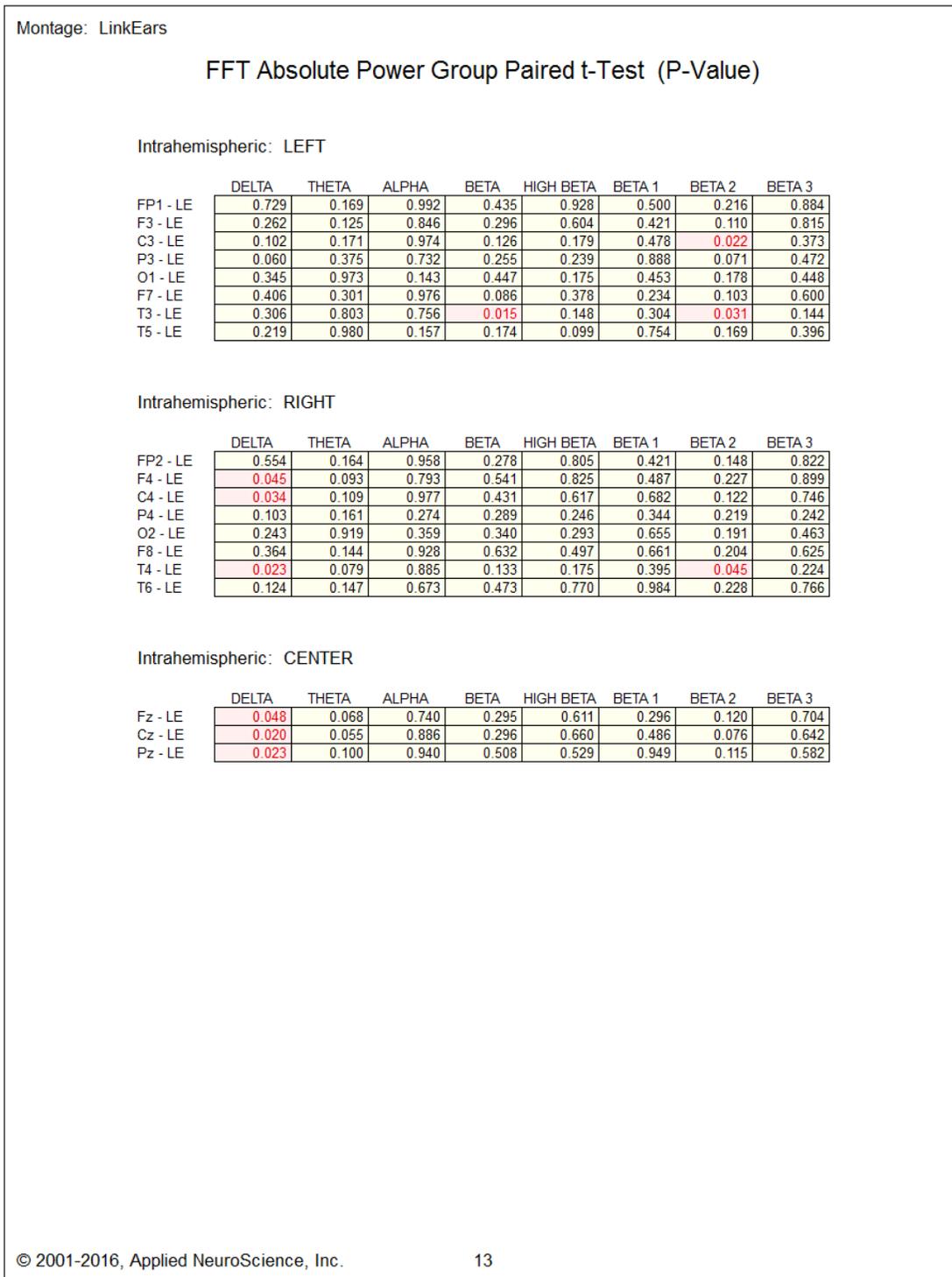


Figure 4. Group Paired T-Test Coherence

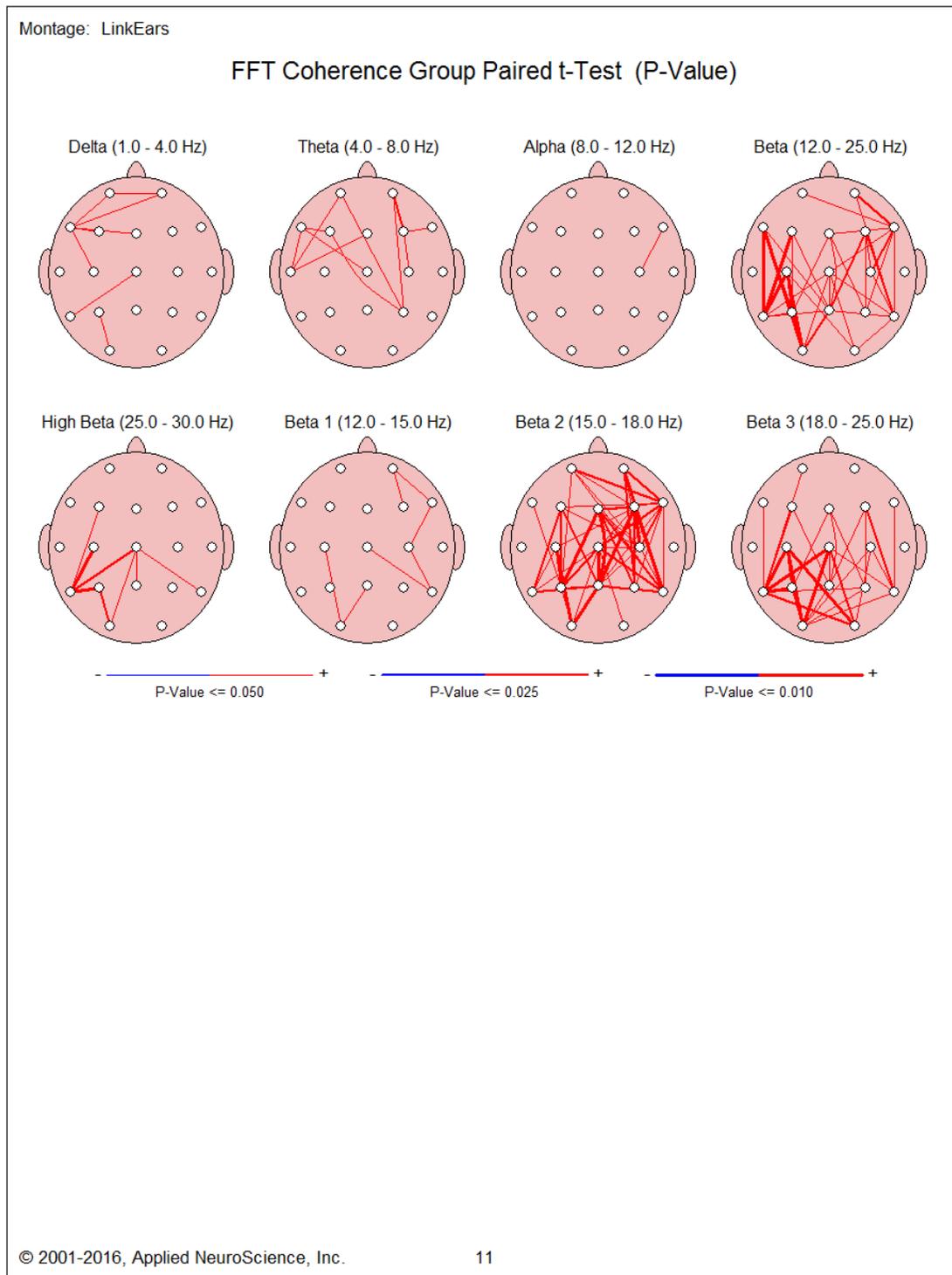


Figure 5. Group Paired T-Test

