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Quantitative EEG Neurometric Analysis–Guided Neurofeedback Treatment in Postconcussion Syndrome (PCS): Forty Cases. How Is Neurometric Analysis Important for the Treatment of PCS and as a Biomarker?

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Abstract

Postconcussion syndrome (PCS) has been used to describe a range of residual symptoms that persist 12 months or more after the injury, often despite a lack of evidence of brain abnormalities on magnetic resonance imaging and computed tomography scans. In this clinical case series, the efficacy of quantitative EEG–guided neurofeedback in 40 subjects diagnosed with PCS was investigated. Overall improvement was seen in all the primary (Symptom Assessment-45 Questionnaire, Clinical Global Impressions Scale, Hamilton Depression Scale) and secondary measures (Minnesota Multiphasic Personality Inventory, Test of Variables for Attention). The Neuroguide Traumatic Brain Index for the group also showed a decrease. Thirty-nine subjects were followed up long term with an average follow-up length of 3.1 years (CI = 2.7-3.3). All but 2 subjects were stable and were off medication. Overall neurofeedback treatment was shown to be effective in this group of subjects studied.

Keywords

postconcussion syndrome (PCS), traumatic brain injury, neurofeedback, QEEG, neurometric analysis, EEG biofeedback, Traumatic Brain Index, TBI

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Introduction and Background

When the head is dealt a blow, and/or is accelerated/decelerated suddenly the skull and the brain can be subject to different forces that result in a traumatic brain injury (TBI). Each year, 1.5 million Americans sustain a TBI, with a new case added every 21 seconds, which leads to 80 000 new cases of long-term disability and 50 000 deaths,[1] and those who have sustained TBI live with the disabilities it causes.

Postconcussion syndrome (PCS) is the name given to long-lasting symptoms that follow a mild head trauma that persist 12 months or more after the injury. Yet, a significant number of patients report persistent symptomatology for weeks or months[2] and some for decades after injury.[3-11] Among the reported symptoms of PCS are cognitive symptoms ranging from attention deficits, to impaired planning and problem solving, psychological symptoms such as impulsivity, irritability, temper outbursts, changes in affect, and physical symptoms such as impaired balance, headaches, dizziness and in rare cases, paranoia and psychosis.[6,9,12-16] Studies on the psychiatric symptoms of PCS show that major depression has been the most studied psychiatric disorder.[17] The rates of axis I disorders in patients with TBI are given in Table 2 later in text.

Studies have found that quantitative EEG (QEEG) is instrumental in predicting the severity of the head trauma. In some cases, it can provide information on the long-term prognosis, and this can be accomplished without any additional information regarding the head trauma (like the Glasgow Coma Score, information on loss of consciousness, etc). Discriminant accuracy as high as 95.67% in the detection of mild head injury[20] and greater than 75.8% accuracy of prediction of outcome 1 year after injury[21] has been demonstrated. These findings have been confirmed with recent studies.[22-28] Discriminant analysis

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between mild and severe TBI groups showed classification accuracy of 96.39%, sensitivity of 95.45%, and specificity of 97.44%.[29]

QEEG also offers the clinician an accurate laboratory test to aid in the detection and differential diagnosis of mood disorders, schizophrenia, and cognitive and attentional disorders [18,30]. Using QEEG discriminant functions, it is possible to differentiate unipolar major depression from normal controls, at a level of 91.3% for both sensitivity and specificity.[31]

According the Vanderbilt Evidence-based Practice Center's review of Traumatic Brain Injury and Depression[32] the strength of evidence for pharmacologic treatment of depression after TBI is lacking. Only 2 publications[33,34] addressed a treatment for individuals diagnosed with depression after a mild traumatic brain injury. Both were studies of antidepressant efficacy, the first being a randomized controlled trial of sertraline, and the second an open-label case series of the effects of citalopram. Neither study showed any significant treatment effect.

Case studies varying between one to nine patients, (the only studies available) of typical antipsychotic medications commonly used to control agitation and psychosis after TBI, showed mixed results [35,36] For posttraumatic epilepsy, results of trials with antiepileptic drugs have been very disappointing. [37]

One modality that has been shown to be effective is neurofeedback (NF). NS is an operant conditioning paradigm whereby patients are given contingent audio/visual rewards for producing specific patterns of brainwave activity. Since the 1960s, studies have shown that through neurotherapy patients can be taught to promote normal functioning in the brain by normalizing dysfunctional brainwave patterns.[38] NF has also been found to improve cognitive and executive functions, memory, motor recovery, attention[39,40] and seizures following TBI,[1,41-47] anxiety,[48] depression,[49-53] schizophrenia,[54] obsessive-compulsive disorder,[55,56] and migraine.[57] A recent study conducted by Munivenkatappa et al[58] reported a significant increase in cortical gray matter volumes, fractional anisotropy, and cortical white matter tracts in TBI patients as did Ghaziri et al,[59] who demonstrated similar results in normal subjects. Recent articles have also shown the marked improvements of cognitive function, magnetic resonance imaging (MRI) abnormalities, and quality of life of TBI patients.[60]

Using evidence-based criteria, the Association for Applied Psychophysiology has developed criteria for setting the level of evidence for efficacy.[61-63] Based on the studies reported to date, TBI NF training can be classified as level 3—probably efficacious—indicating the availability of multiple observational studies, clinical studies, wait list controlled studies, and within subject and intrasubject replication studies that demonstrate efficacy. This classification was based on studies conducted by Keller,[64] Schoenberger et al,[65] Tinius and Tinius,[42] Thornton,[66] and Walker et al.[43] studies. However, in a review of NF studies, May et al[67] concluded that all studies demonstrated positive findings, in that NF led to improvement in measures of impairment, whether subjective, objective, or both. However, placebo-controlled studies were lacking, some reports omitted important details, and study designs differed to the point where effect size could not be calculated quantitatively. This review, however, did not include 2 key controlled studies using NF in TBI.[68,69] Recent articles have also shown marked improvements of cognitive function, MRI abnormalities, and quality of life of TBI patients.[70]

Because of the above listed effects of NF the current study was conducted to investigate the following:

How subjects with mild TBI or PCS in their history are diagnosed (axis I-II disorders), treated (with medication or unmedicated), and what is the outcome of their treatment, in a conventional clinical setting?
By using QEEG neurometric analysis as a biomarker, the possibility of differentiating mild TBI or PCS from other axis I (eg, depression, bipolar disorder, schizophrenia) disorders.
If this group could benefit from QEEG-guided and individualized NF treatment in a clinical setting, without any other treatment.
Can the changes in the subject's symptomatology, induced by NF training, be measured objectively using validated measures (Symptom Assessment-45 Questionnaire, Hamilton Rating Scale for Depression, Minnesota Multiphasic Personality Inventory, Clinical Global Impressions Scale, Test of Variables for Attention, and QEEG)?
Do the changes due to NF last past the end of the treatment and if so how long can they be observed?

Materials and Methods

The study included 40 subjects who signed an informed consent for NF treatment. The subjects were recruited from a clinical population who came to our center specifically to receive NF treatment. The Texas State Health Maintenance Organization mandated that NF treatment be included in the coverage for brain injury/acquired brain injury[71] and the Turkish Ministry of Health has included biofeedback as an approved outpatient treatment procedure.[72] For these reasons, this clinical study was not submitted to a medical ethics committee.

The mean age of the subjects was 28.9 years (CI = 26.4-34.4). There were 40 subjects in all, of whom 23 were male (mean age 28.6 years, CI = 25.6-34.6) and 17 were female (mean age 29.2 years, CI = 24.8-33.7). All the subjects were in the chronic or nonacute postinjury period when they were evaluated and had symptoms that manifested after the TBI, and were not effectively treated. The average interval between TBI injury and QEEG and neuropsychological evaluations was 11.8 years (range 0-30 years). All subjects were systematically asked the following questions:

Have you ever suffered a small or heavy blow to your head?
Have you ever lost consciousness?
Have you ever hit your head hard enough to see stars or be dazed for a couple of minutes? Have you ever had a car accident? Have you ever crashed into something and if so

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did your head moved back and forth? When playing sports were you ever hit on the head or have you hit your head and/or bumped heads (soccer, boxing, jumping on a trampoline, sledding, skiing, etc)?

Inclusion Criteria

All subjects were required to have had at least one head trauma, with or without loss of consciousness.

Subjects may have a diagnosis of one of the axis I psychiatric diagnosis as defined by *DSM-IV* criteria before coming to us and the psychiatric symptoms must have started after the head trauma. According to *DSM-IV*, an axis I or axis II disorder is invalidated if a medical condition like a head trauma exists (DSM-IV, 1994).

QEEG neurometric analysis (Food and Drug Administration [FDA]–approved NxLink and NeuroGuide) had to suggest a PCS, confirmed by the clinical judgment of the evaluating physician. QEEG NxLink neurometric analysis should not suggest any similarity to any other discriminant (according to the symptoms the QEEGs were compared with the other discriminants, such as depression, bipolar disorder, attention deficit/hyperactivity disorder (ADHD), learning disability, schizophrenia, and substance abuse).

No other treatment was administered during NF treatment.

No other concurrent medical condition as determined by history and laboratory tests (hemogram, thyroid-stimulating hormone, B12, B6, folic acid, electrolytes, liver enzymes and total cholesterol panel).

Exclusion Criteria

The exclusion criteria were the following:

Subjects not meeting the aforementioned criteria
Fully psychotic subjects
Subjects at risk of suicide
History of medical conditions that would place subject at significant risk by participating in the neurofeedback treatment.

Demographic, Medical, and Symptom Information

The summary of the 40 subjects are given in Table 1.

Previous Diagnosis

All the subjects except one were diagnosed with a psychiatric disorder previously, and had sought treatment elsewhere. One subject was told nothing was wrong with him. When the subjects sought treatment, none of them reported being asked if they had a head trauma or not by the psychiatrists that previously treated them. None of the subjects themselves thought that their head trauma was the cause of their problems and did not volunteer information about their head trauma unless specifically asked. The previous diagnoses and their frequencies of occurrence are presented in Table 2.

Previous Treatments

A tabulation of the drugs taken over the subject's lifetime show that 66% these subjects received some sort of psychotropic treatment at one point or another. The average drug treatment duration was 15.1 months (CI = 10.0-20.2). At the time of admission, 27% were taking a psychotropic, and some of them (9%) were prescribed more than one psychotropic. Of the drugs that the subjects were taking, the most frequently prescribed were antidepressants (40% over the lifetime and 44% at the time of admission) followed by antipsychotics (32% and 20%, respectively) and anticonvulsants (8% and 15%). When the frequency of drugs prescribed was tabulated it was observed that for this disorder 30 different drugs were prescribed. Of these citalopram was the most frequent medication prescribed (11% of the time) followed by ketiapine (8% of the time), paroksetine HCl, and sertraline (6% of the time).

MRI Findings

For the subjects whose MRI results were available, 9 subjects had negative findings. Of these 9 subjects, 4 were found to have cerebral atrophy, 4 had prominence of the sulci, and 1 had an enlargement of the ventricles and sulci.

Data Collection

Data were collected from 40 subjects. One subject dropped after 40 sessions of NF treatment. This subject had a seizure disorder that developed after his head trauma and was allowed to be on antiepileptic medication. Because of improvements in the frequency and intensity of seizures as well as improvements in mood, obsessions, aggressive outbursts and socialization the subject was included in the data.

The outcome measures consisted of the Symptom Assessment-45 Questionnaire (SA-45), a measure of treatment outcome for psychiatric populations (SA- 45, 2000), The Hamilton Rating Scale for Depression (HAM-D, 1960), Clinical Global Impressions Scale (CGI), the Test of Variables for Attention (TOVA) and the Minnesota Multiphasic Personality Inventory (MMPI). These tests were administered at baseline and except for the MMPI every 20 sessions. The repeat MMPI was administered at the end of treatment. The CGI was evaluated by a medical doctor and the MMPI and TOVA were administered by a trained neuropsychologist. Both were blinded with regard to the subjects' protocol and diagnosis.

Although all subjects were administered the MMPI and TOVA, data were not obtained from those subjects that at pretreatment would not take these tests or performed in a way that invalidated the results. Of the 40 subjects, MMPI and TOVA data were obtained from 29 and 38 subjects, respectively.

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Table 1. Demographic Information.

Subject	Sex	Age, y	HT Description	LOC	Symptoms of Disease	Age at time of HT	Initial Diagnoses	Paranoia	Visual Hallucinations	Auditory Hallucinations	Anger Aggression	HT Age	Age at Initial Diagnosis
1	M	32	7-8 y, fell from 2 m. MVA where he hit a pole at 110 km/h	Y	Y	7-8, 26	Partial epilepsy, ADHD	N	N	N	Y	7-8, 26	26
2	M	21	Hit on head when playing with friends, HT while playing soccer	N	N	12	Depression	N	N	N	Y	12	16
3	M	45	Fall from tree and MVA	N	N	11-12 and 24	Insomnia	Y	Y	Y	Y	11-12 and 24	32
4	F	23	Hit head. Fell from high wall	N	N	7 and 10	Insomnia, poor impulse control	Y	N	N	Y	7 and 10	20
5	F	38	Vacuum birth. Fell on stone surface. Beating requiring hospitalization. Fell on back of head with LOC. MVA	Y	Y	0, 1.5 19, 22, 34	Bipolar disorder	N	N	N	N	0, 1.5 19, 22, 34	38
6	F	23	Fell on back of head without LOC	N	N	17-18	Generalized anxiety disorder, depression	Y	N	Y	Y	17-18	20
7	F	22	Vacuum birth. Hit by ball. Hit on the back of the head numerous times	N	N	10	Depression	Y	N	N	N	10	22
8	F	23	Dove into a pool from 2 m and hit head. Was dazed	Y	N	7	PCS	Y	N	N	Y	7	23
9	F	26	MVA with confusion and dizziness	Y	N	17	Depression	N	N	N	Y	17	23
10	M	22	Fell from crib. Fall from slide breaking collarbone	Y	N	6m, 3	Never diagnosed	Y	N	N	Y	6m, 3	10
11	F	30	Shrapnel in face	Y	N	22	Depression	Y	N	N	Y	22	29
12	F	20	Fell from crib as a baby on hard surface. MVA hit head on console. Hit head on ceiling when jumping on bed. Fell on head while attempting a handstand. Hit head while diving off a pier	N	N	3 mo, 2, 4-5, 9, 12	ADHD	Y	N	N	Y	3m, 2, 4-5, 9, 12	13
13	M	33	Hit on the head with a ball, was dazed. Hit on head during an assault	N	N	8, 31	Depression	N	N	N	Y	8, 31	8
14	F	19	Hit on head with basketball and was dazed. Hit on head with soccer ball	N	N	8, 10	Depression, OCD	Y	N	N	Y	8, 10	18
15	F	31	Fell twice from the top bunk on head. Hit head on window pane. Mother threw her against the wall	N	N	6,8,12	Depression	N	N	N	N	6,8,12	24
16	F	26	Hit by a car	N	N	10	Depression, generalized anxiety disorder	Y	N	N	Y	10	25
17	M	31	Fell on left side and what he was carrying stuck in his head. Fell on the back of his head	N	N	5-6, 9-10	Nothing wrong	Y	N	N	Y	5-6, 9-10	26
18	M	22	Nail in head. Hit by ball dazed. Numerous hits on head	N	N	6, 10. 15	OCD	N	N	N	Y	6, 10. 15	21
19	F	26	Fell from balcony and cracked skull	Y	N	2	Depression	Y	N	N	Y	2	11
20	M	23	Severe fall on back of head	Y	N	13	Depression	Y	N	N	N	13	19

(continued)

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Table 1. (continued)

Subject	Sex	Age, y	HT Description	LOC	Symptoms of Disease	Age at time of HT	Initial Diagnoses	Paranoia	Visual Hallucinations	Auditory Hallucinations	Anger Aggression	HT Age	Age at Initial Diagnosis
21	M	21	Fell from bike on head	N	N	4-5	Depression, stuttering	N	N	N	N	4-5	17
22	M	30	Hit on back of the head with a metal piggy bank. Hit on head with ball. Fell from slide on head	N	N	5-6, 6-7, 8	Major depression, anxiety	N	N	N	Y	5-6, 6-7, 8	8
23	M	40	Fell on head from 1.5 m	Y	N	14	Depression	N	N	N	Y	14	17
24	M	41	Fell on stairs. Fell out of car on head	Y	N	5, 23	Alcohol abuse	N	N	N	N	5, 23	7
25	M	30	Fell on head	N	N	3m	Depression	Y	N	N	Y	3m	19
26	M	20	Severely bumped heads and fell on head	Y	N	12	Depression	N	N	N	Y	12	14
27	M	19	Fell down stairs. Hit by car and was flipped. Hit on head by ball, was dazed	Y	N	9-10	OCD, panic disorder	Y	N	N	Y	9-10	13
28	F	44	Hit on head with ball and was dazed	N	N	10	Migraine	N	N	N	Y	10	40
29	M	31	Hit back of the head on radiator. Hit in the face with a football	N	N	10-12, 17	Depression, bipolar disorder, OCD	N	N	N	Y	10-12, 17	24
30	F	38	Fell on head. Hit on head and bleeding from brow and head	Y	Y	1 mo, 10	Depression	Y	N	Y	Y	1m, 10	34
31	M	30	Hit on head with soccer and was dazed. MVA where car was flipped at high speed	N	N	8-9, 12	Depression	N	N	N	Y	8-9, 12	27
32	M	22	Fell on head	N	N	6-7	Panic attack	N	N	N	N	6-7	21
33	F	53	Fell from balcony stairs. MVA	Y	N	9, 50	Depression	Y	N	N	Y	9, 50	51
34	M	32	Fell from bike on head	N	N	15-16	OCD	Y	N	Y	Y	15-16	28
35	F	19	Cabinet fell on head. Fell from tree	N	N	2-3, 4	Bipolar disorder	N	N	N	Y	2-3, 4	16
36	F	33	Fell from stairs. MVA	Y	N	3, 20	Depression	N	N	N	Y	3, 20	31
37	M	22	Hit head when doing a flip off a wall	Y	N	8-9	Mood disorder, poor impulse control	N	N	N	Y	8-9	18
38	M	22	Fell numerous times on head	N	N	0-1, 7	Depression	Y	N	N	N	0-1, 7	7
39	M	22	Hits head on wall when angry. Hits head numerous times in street fights. MVA	N	N	10-16	Drug abuse	Y	N	N	Y	10-16	10
40	M	29	Hit head when he first started to walk. MVA	N	N	1, 6	Depression, drug abuse	N	N	N	Y	1, 6	6

Abbreviations: ADHD, attention deficit/hyperactivity disorder; F, female; HT, head trauma; LOC, loss of consciousness; M, male; MVA, motor vehicle accident; N, no; OCD, obsessive-compulsive disorder; Y, yes.

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Table 2. Previous Diagnoses the Subjects Received.[a]

Diagnosis	Number of Subjects With			Total	Percent	Reported Prevalence in Literature (%)
	Primary Diagnosis	Secondary Diagnosis	Tertiary Diagnosis			
Depression	22	1	0	23	45	14-77
Obsessive-compulsive disorder	3	1	1	5	10	2-15
Bipolar disorder	2	1	0	3	6	2-17
Anxiety	1	2	0	3	6	3-28
Substance abuse	2	1	0	3	6	5-28
Insomnia	2	0	0	2	4	30-50
Panic attack	1	1	0	2	4	4-17
Poor impulse control	0	2	0	2	4	12-33
Mood disorder undifferentiated	1	0	0	1	2	NA
Seizure disorder	1	0	0	1	2	7-11
Attention deficit/hyperactivity disorder	1	0	0	1	2	19-48
Attention problems	1	0	0	1	2	2-4
Postconcussion syndrome	1	0	0	1	2	3-27
Never diagnosed	1	0	0	1	2	NA
Nothing wrong	1	0	0	1	2	NA
Migraine	1	0	0	1	2	18-33
Stuttering	0	1	0	1	2	NA
Psychosis/paranoia	0	11	9	20	50	6

References: major depression,[16,72-78] dysthymia,[15,16,74,78] bipolar disorder,[75,77,78,80] generalized anxiety disorder,[16,73,77,79,81] panic disorder,[15,16,77,78] obsessive-compulsive disorder, phobic disorder,[80,81] posttraumatic stress disorder,[80-82] schizophrenia,[75,81] attention deficit/hyperactivity disorder,[83] insomnia,[84-86] impulse control,[87] seizure disorder,[88] attention,[89] migraine,[90] psychosis.[91]

A pretreatment medication-free QEEG was recorded eyes closed, resting, using a Lexicor Neurosearch-24 QEEG system (software version 3.10) with a 128 pps sampling rate. For each of the 40 subjects by a medical doctor trained in electrophysiology where the FDA registered NxLink,[92-94] and NeuroGuide[20,21,29] QEEG databases were used.[92] To ensure that all drugs had cleared the system, all subjects were washed out for up to 7 half-lives of the medications they were taking (eg, if they were on risperidone, the 7 half-lives of the medication is 6 days, so QEEG was recorded on the day 7). For the analysis, at least 60 seconds of artifact-free EEG samples were selected and were analyzed using NeuroGuide software of Applied Neurosciences Inc, which calculates the EEG discriminants and compares them against a database of TBI patients. All of the subjects classified as having electrophysiological similarity to the TBI database. The comparison also yields a measure called the Traumatic Brain Injury Index, which is a number between 1 and 10 indicating the severity of the TBI based on a discriminant classification, where 1 to 3 can be considered as mild, 3 to 5 as moderate, and >5 as severe head trauma.[29] The TBI Index was not used as an inclusion criterion, but was used biomarker to monitor changes (if any) induced by the treatment. Using the same method, all the subjects' EEGs were compared against the NxLink database to rule out a mood disorder or schizophrenia and can also be used as a biomarker for the disorder. None of the subjects' QEEGs classified as being similar to the NxLink mood disorder, ADHD, or the schizophrenia cohort.

The electrodes were applied using an Electrocap by ElectroCap International. Nineteen channels were recorded in the eyes-closed condition with the subject reclining in a resting position. Ten minutes were recorded and during the recording artifact and vigilance control was performed by a trained electrophysiologist medical doctor who was blinded as to the diagnosis and the treatment protocol selected for the subjects. After the recording, an artifact-free 1-minute sample was selected from the 10-minute recording to be submitted by the normative comparison software. The selection was done by the first author who is a board-certified QEEG expert. The selected samples were compared against the NxLink database both before and after treatment as well as every 20 sessions, in order to reveal the divergence of the brain electrical activity from norms, in the form of *Z* scores and to guide the NF treatment protocols by training the areas that show deviations from normal, as determined by the comparisons to the NxLink database. In neurometric QEEG analysis, all QEEG variables are calculated as *Z* scores, which are scores equal to the distance (deviation) from the norm in standard deviation (SD) units. The rationale behind this approach is that the participants who normalize their QEEG *Z* scores will benefit the most from NF treatment.[95-97]

Each treatment was personalized to each subject, and regularly monitored and adjusted for optimum treatment effect. The ultimate goal of the training was to keep administering sessions until the subjects' symptoms either disappeared or were diminished enough that they do not affect the subject's quality of life.

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Table 3. Neurofeedback Training Protocols.

Targeted Symptom	Leads	Reward Parameters	Comments
Coherence training	FP1, FP2	Alpha coherence inhibit	Hypercoherence can be considered as a lack of differentiation of brain functions or as a decrease in flexibility of functioning[96]
	F3, F4	Alpha inhibit	
	C3, C4	Beta (21-32 Hz) inhibit	
	P3, P4	Beta coherence inhibit	
	T3, T4	Beta (13-32 Hz) inhibit	
	O1, O2	Delta inhibit	
	FP1, FP2	Theta coherence inhibit	
	F3, F4	Theta inhibit	
	C3, C4	Beta (13-32 Hz) inhibit	
	P3, P4		
	T3, T4		
Attention, motivation, inhibition of emotions, depressive symptoms	Fp1-Fp2	Inhibit Alpha	The frontal and fronto-temporal electrode sites below were selected according to the subjects' QEEG[97]
	Fp1-F3	Inhibit Delta	
	F3	Inhibit Theta	
	C3		
Calming effect, sleep	Cz-C4	Reward sensorimotor rhythm Inhibit Theta or Alpha	The sensory area is usually used for its calming effect and is also helpful in sleep[99]
Obsessive-compulsive disorder symptoms	F3	Inhibit Alpha or Beta,	This has been found to be useful in obsessive-compulsive disorder[55]
	Fz	Inhibit Delta	
	F4	Inhibit Theta	
	P4		
Auditory hallucinations	F7-T3	Inhibit Alpha	Evidence from functional MRI studies conducted also showed that subjects with auditory hallucinations significantly lower connectivity between left temporal cortex and left dorsolateral prefrontal cortex.[19,100] We have used this area in a large scale schizophrenia study[54]
	T3-T4	Inhibit Theta	
Visual hallucinations	O1-O2	Inhibit Theta	These sites have been found to helpful in visual hallucinations[54,99]
	P3-P4	Inhibit Delta	
Paranoia	F7-T3	Inhibit Alpha Inhibit Theta Inhibit Beta	This site has been found to helpful in visual hallucinations[54,99]

Treatment Protocols

All the NF training was performed using FDA-registered Thought Technology Infinity (version 6). Each session lasted 60 minutes with a 5-minute break after 30 minutes of training. Sessions were administered daily. The sessions were administered by a MS psychologist with 10 years of neurofeedback experienced and was supervised by the first author who is a Biofeedback Certification International Alliance (BCIA)–certified Associate fellow.

The NF system presents the user with real-time feedback on brain wave activity, typically in the form of a video display and sound aiming to provide real-time information to the central nervous system (CNS) as to its current activity. When the desired paradigm is accomplished, the subject is rewarded with a moving display and/or a sound. Manual thresholding was used to ensure learning.

All sessions were recorded eyes open unless an Alpha increase protocol was being used. Training sites were selected based on the QEEG analysis (using the NxLink database). The location of the deviant Z scores is most important no matter what the EEG measure with the goal of linking the subject's symptoms to deviant *Z* scores (greater than and less than 1.96) located in regions of the scalp related to functional specialization in the brain and the subject's symptoms.[95]

The electrode application was based on the international 10-20 system. Since changes in EEG coherence and EEG phase delays, which are linearly related to the magnitude of injury to both the gray matter and the white matter, especially in frontal and temporal lobes[98] hypercoherence (areas that show increased coherence in comparison with norms) revealed by the QEEG analysis was targeted first, followed by areas showing increased relative power activities. This was done in sequence for all targeted brain areas. Table 3 is a general summary of training protocols used for the study.

The criteria used to shift from one site to another were the *Z* scores of the QEEG, which was supplanted with the first author's clinical experience.

The mean number of sessions completed by the subjects was 48.0 (CI = 42.0-54.0.) sessions within 19 days to 94 days. Although all subjects were encouraged to come for their sessions daily (6 days a week) subjects that could not keep this schedule ended up lengthening their total training period.

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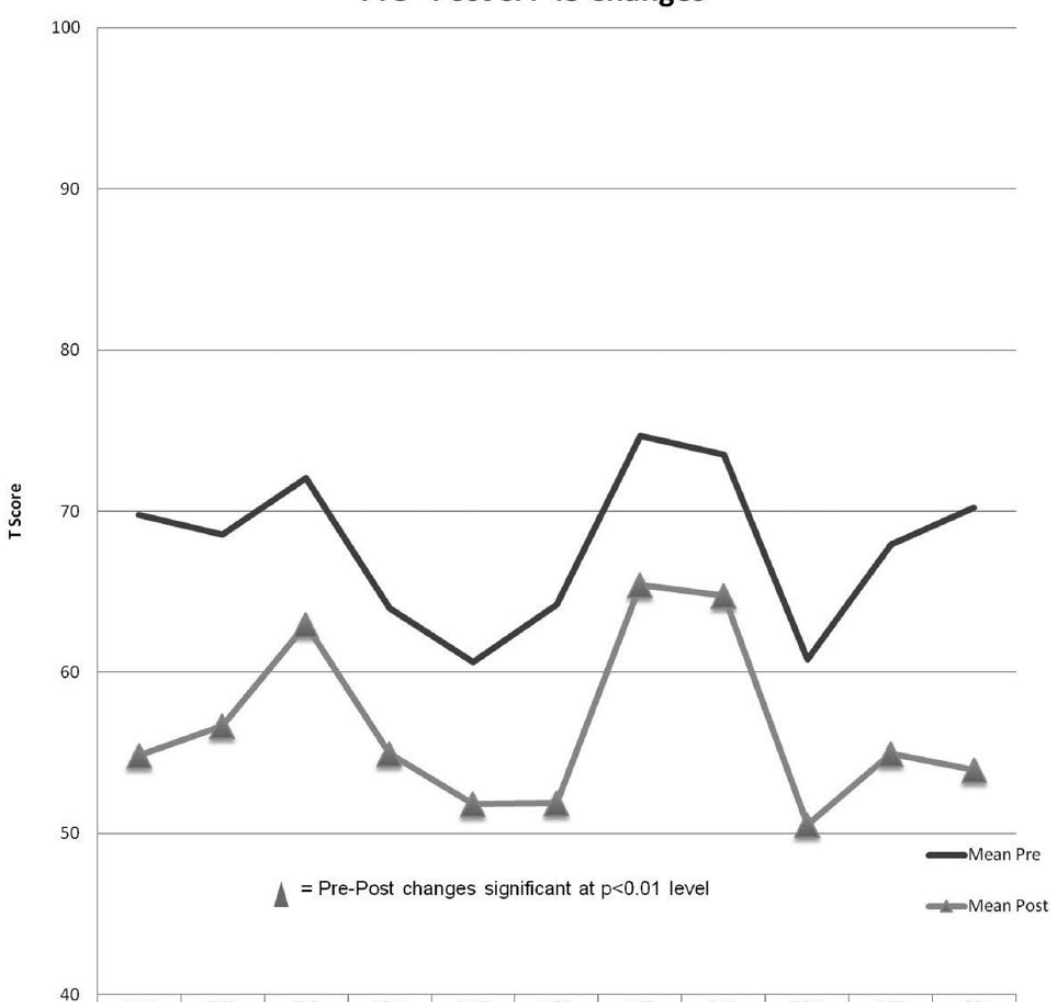

	ANX	DEP	OC	SOM	PHO	HOS	INT	PAR	PSY	PST	GSI
Mean Pre	69.78	68.55	72.08	64.00	60.63	64.20	74.70	73.50	60.80	67.93	70.23
Mean Post	54.85	56.68	62.95	54.98	51.85	51.90	65.45	64.75	50.55	54.98	53.93
StDev Pre	11.50	8.42	7.34	9.88	9.80	10.88	9.30	7.49	8.66	9.24	10.61
StDev Post	9.36	6.91	7.04	6.86	6.44	6.46	6.36	5.88	5.97	12.12	10.58
Change	-14.93	-11.88	-9.13	-9.03	-8.78	-12.30	-9.25	-8.75	-10.25	-12.95	-16.30
F(1,39)	77.73	61.13	63.11	62.69	31.54	37.79	43.40	56.30	62.43	61.79	88.76
η2(1,39)	0.67	0.61	0.62	0.62	0.45	0.59	0.53	0.59	0.62	0.61	0.69

Figure 1. Pre to post SA-45 (Symptom Assessment–45 Questionnaire) changes.

Long-Term Follow-up

In order to assess the permanence of the NF treatment all subjects were followed-up for up to 5 years (where possible) by either regular in-clinic interviews and/or with interviews over the phone. MS psychologists familiar with the subjects conducted these interviews with the subject and the subject's family.

Statistical Analysis

The collected data were sent for analysis to an independent statistician, who did not have any contact with the subjects. Pre- and posttreatment changes were assessed using repeated-measures analysis of variance (ANOVA) with correction for intrasubject variability.

Results

SA-45 Results

The results of all the SA-45 (see Figure 1) show a statistically significant reduction ($P < .01$) of all clinically significant deviant scores (T score >60), based on a repeated-measures ANOVA with correction for intrasubject variability.

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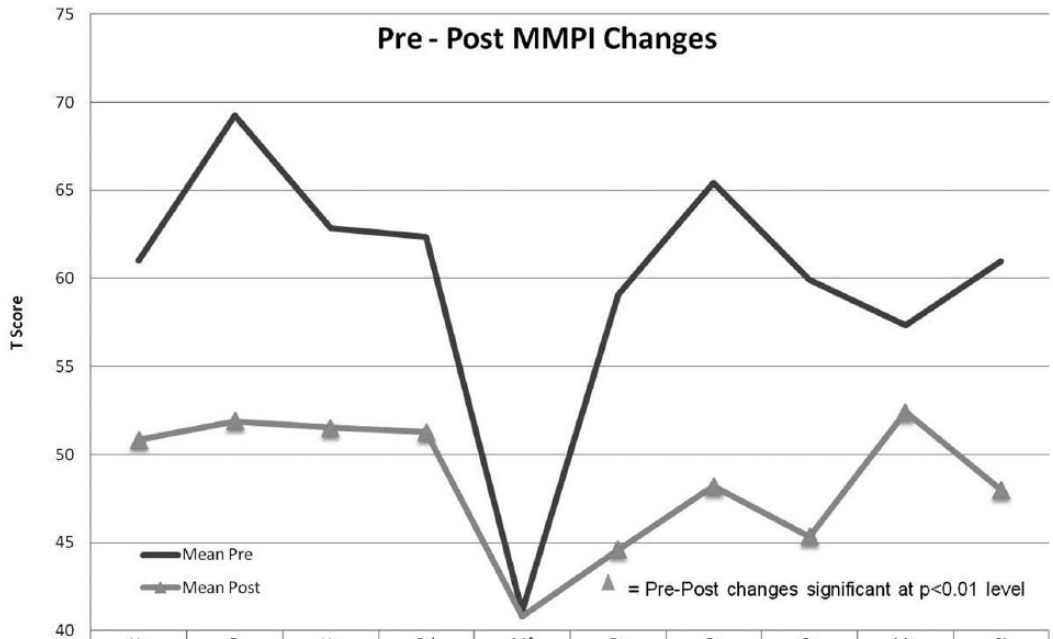

	Hs	D	Hy	Pd	Mf	Pa	Pt	Sc	Ma	Si
Mean Pre	61.03	69.24	62.83	62.38	41.14	59.10	65.45	59.93	57.34	60.97
Mean Post	50.83	51.90	51.52	51.28	40.83	44.59	48.21	45.34	52.41	48.00
StDev Pre	12.41	13.67	11.69	11.88	11.69	13.57	11.67	12.12	11.04	15.73
StDev Post	7.83	11.15	9.98	9.02	9.62	8.64	9.22	6.67	8.24	14.15
Change	-10.21	-17.34	-11.31	-11.10	-0.31	-14.52	-17.24	-14.59	-4.93	-12.97
F(1,28)	23.10	23.56	27.70	20.30	0.03	33.36	0.66	38.88	7.08	26.36
η2(1,28)	0.45	0.46	0.50	0.42	0.00	0.54	0.66	0.58	0.20	0.48

Figure 2. Pre to post MMPI (Minnesota Multiphasic Personality Inventory) changes.

HAM-D Results

The group as a whole had a mean HAM-D score of 15.58 (CI = 13.16-17.99), which is equivalent to a moderate level of depression. At the end of the study, the mean HAM-D score was 0.55, (CI= −0.10 to 1.20), a 15.03 point decrease, which was found to be significant at the $P < .01$ level of significance using an ANOVA with correction for intersubject variability: $F(1, 38) = 148.28$, $\eta^2(1, 38) = 0.79$. Thirty-seven (93%) subjects had no depressive symptoms at the end of the study and therefore their HAM-D score was rated as being 0.

MMPI Results

An MMPI was administered to all subjects before treatment and after completion of treatment, however, results were only available for 26 out of the 40 subjects because of the fact that a baseline MMPI could not be administered and/or was invalid due to some subjects' mental state at the time of the test. The MMPI results are summarized in Figure 2 and Table 4. As can be seen all scores except the Masculinity-Femininity score, show a decrease after treatment, which was significant at a $P < .01$ level of statistical significance based on a repeated-measures ANOVA taking intrasubject variability into consideration.

In order to assess the individual improvements, the number of subjects who had a significant score (>70) was tabulated for each of the parameters both for pre- and poststudy measurements (see Table 4).

The results show that the number of subjects who have significant parameter scores decreased after treatment. Except for MF, which did not have any scores >70, all the scores showed a decline in the number of significant scores. The parameter with the highest number of significant scores was depression (14 or 46% of the subjects) followed by Psychasthenia (12 or 41% of the subjects), followed by Hysteria (8 or 28% of the subjects) and Psychopathic Deviation (7 or 24%). The subjects who had significant scores in Paranoia, Schizophrenia, and Mania (6, 4, and 2, respectively) did not show any significant scores after treatment.

TOVA Results

The Test of Variables of Attention (TOVA) is a continuous performance test designed to objectively measure attention, impulsivity and adaptability in a clinical setting with norms for ages from 4 to 80+, by providing an objective measurement. The results of the TOVA test are reported as standard scores (average standard = 100; SD = 15). Standard scores >85 are considered to be in the normal range, scores between 80

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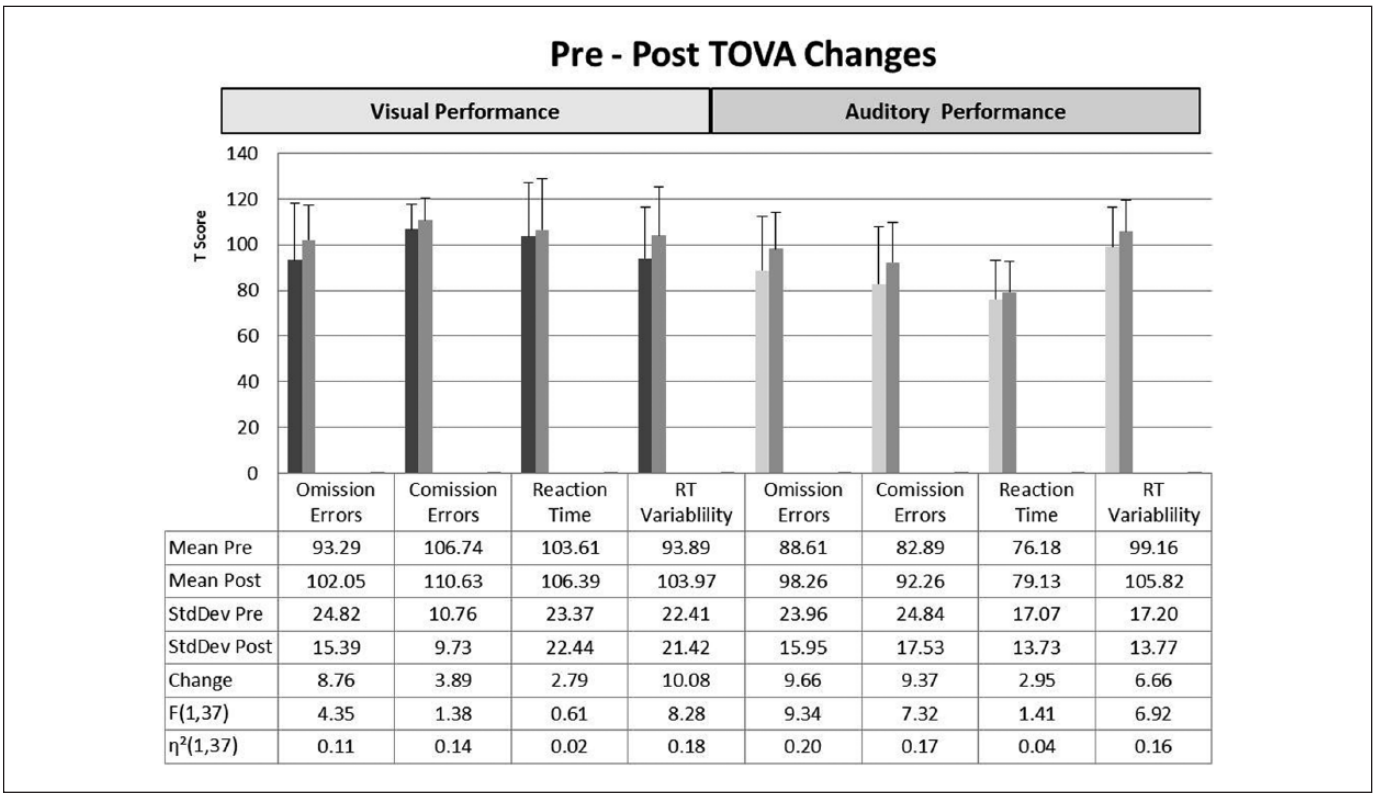
Table 4. Changes in the Number of Significant (>70) MMPI (Minnesota Multiphasic Personality Inventory) Scores.

	Hs		D		Hy		Pd		MF		Pa		Pt		Sc		Ma		Si	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Pre	7	24	14	46	8	28	7	24	0	0	6	21	12	41	4	14	2	7	7	24
Post	0	0	4	14	1	3	0	0	0	0	0	0	1	3	0	0	0	0	2	7

Abbreviations: Hs, hypochondriasis; D, depression; Hy, hysteria; Pd, psychopathic deviate; MF, masculinity/femininity; Pa, paranoia; Pt, psychasthenia; SC, schizophrenia; Ma, hypomania; Si, social introversion.



	Omission Errors	Comission Errors	Reaction Time	RT Variablility	Omission Errors	Comission Errors	Reaction Time	RT Variablility
Mean Pre	93.29	106.74	103.61	93.89	88.61	82.89	76.18	99.16
Mean Post	102.05	110.63	106.39	103.97	98.26	92.26	79.13	105.82
StdDev Pre	24.82	10.76	23.37	22.41	23.96	24.84	17.07	17.20
StdDev Post	15.39	9.73	22.44	21.42	15.95	17.53	13.73	13.77
Change	8.76	3.89	2.79	10.08	9.66	9.37	2.95	6.66
F(1,37)	4.35	1.38	0.61	8.28	9.34	7.32	1.41	6.92
η^2(1,37)	0.11	0.14	0.02	0.18	0.20	0.17	0.04	0.16

Figure 3. Pre to post TOVA (Test of Variables of Attention) changes.

and 85 are considered borderline, and scores <80 are outside normal limits. Scores <70 are considered significantly below normal ranges.[101] TOVA was conducted at baseline and after treatment. In this group, the visual TOVA scores of the subjects were within normal ranges at baseline. As the results given in Figure 3 show, there is a consistent improvement in performance (since the values are *T* scores increasing *T* scores indicate improved performance). However, this improvement was not statistically significant for the reaction time. The auditory values show increases that were more significant. What can also be observed is that the omission errors and reaction time variability show greater improvement.

Clinical Global Impressions

The CGI was scored by a physician who was blinded as to the subject's status and treatment. The group's mean CGI severity score was 6.10 (CI = 5.8-6.4) before treatment and 1.90 (CI = 1.7-2.1) after treatment. This was found to be significant at the $P < .01$ level based on a *t* test.

QEEG Results

The pretreatment QEEG shows that the majority of the subjects (73%) had increased Alpha activity (in comparison with norms), and that 45% had increased coherence. The remaining percentages are as follows: Theta 5 (13%), Beta 3 (8%), Theta/Beta, Theta/Alpha 2 (3%). After treatment, the TBI Index values changed from a moderate level (5.00, CI = 4.73-5.28) to a mild level (3.10, CI = 2.43-3.78), which was found to be significant using an ANOVA taking into account intersubject variability: $F(1, 39) = 33.43$, $\eta^2(1, 39) = 0.46$, $P < .001$. From the group, 12 (29%) subjects decreased their scores from a mean of 4.89 (CI = 4.40-5.16) to 0.

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Side Effects and Adverse Events

No adverse events, side effects and/or any unpleasant feelings were reported by any of the subjects throughout their training.

Long-Term Follow-up

A long-term follow-up over the phone was conducted on all subjects. Of the 40 subjects, 39 were reached. The average follow-up duration was 3.1 years (CI = 2.7-3.3) after treatment. All except 2 subjects (5%) reported being fine (95%) with no complications and none of them sought psychiatric help after their NF treatment. None of the subjects were taking any medication. One subject who had positive changes after NF treatment did not attribute her improvement to NF and at the follow-up reported no positive changes. Another subject also had positive changes after NF treatment, but at the time of the follow-up also did not attribute his improvement to NF and stated that he did not feel the need to seek medical help again.

Discussion

The results of this study show that based on the initial hypothesis, conventional treatment did not benefit this group of subjects, whereas NF treatment was able to show reduction of symptoms based on the objective measures studied and these changes lasted long after the subjects completed their treatment based on long-term follow-up results.

One objective measure that showed efficacy in this very chronic group of subjects the HAM-D showed a decrease in depression symptoms where the score of the group decreased to 0 from 15.58. The double blind sertraline study of Ashman et al[33] showed response (defined as a decrease of the HAM-D score by 50% or a drop below 10) in 59% of the subjects. Using the same criteria, the response in this study was 95%, and 93% of the group decreased their scores to 0. The group mean was reduced from 15.58 (moderate depression) to 0.55. This is an overall reduction of 15 points, and was found to be significant at $P < .001$ level of significance. Given the effect size of the neurofeedback treatment with 93% to 95% decrease in the Hamilton rating scale to 0 it is difficult to explain such strong effect size based on a placebo factor and this result compares with the double blind study given above.

Another objective measure, the TBI Index derived from the QEEG also showed an improvement, where the subjects went from a moderate level (5.00) to a mild level (3.10). In this study, 12 subjects decreased their score from an average of 4.89 to 0. It has been shown that this index is stable over time (compared with baseline), 6-month, and 12-month repeated testing.[98]

Finally, these changes were also observed by a blinded physician where the CGI went from being markedly ill to mildly ill. The subjects rated themselves as being better (SA-45, MMPI), the physicians were able to see and rate the improvement (HAM-D, CGI) and objective measures confirmed these findings (QEEG, TBI Index, TOVA).

As reported in Table 2, there is a prevalence of psychiatric symptoms in TBI. The SA-45 findings indicate that NF treatment was able to reduce the psychiatric symptoms as demonstrated by the statistical decrease in symptom scores.

An important factor in the identification of these subjects is the head trauma screening and QEEG recording, which is an integral part of the initial patient evaluation. QEEG and Neurometric analysis can be used as a biomarker to provide information to help the clinician differentially diagnose between PCS and an axis I disorder.[98]

Most of these subjects had been unsuccessfully treated. Evidence-based drug data in treating TBI are very sparse and therefore any medication administration is mostly off-label. The greatest disparity in efficacy of prescribed medications between supported and unsupported off-label prescription occurred among psychiatric medications, which includes antidepressants, anxiolytics, and antipsychotics (4% strong support vs 96% limited or no support) and anticonvulsants (17% strong support vs 83% limited or no support).[102] Only 4 subjects (10%) were given drugs (citalopram, sertraline) that were investigated in PCS[33,34] and none of them benefitted from these medications. Before coming to us, the treatment of all but one of the subjects consisted of pharmacological treatment based on their symptoms. In this group of subjects 40% were treated with an antidepressant and 36% with an antipsychotic, even though there are very little data to support their use in PCS. For this reason, new methods of treatment are necessary and QEEG guided NF is one method that seems to be effective.

This study shows that NF treatment, by normalizing the brain's electrical activity, is able to reduce the subjects' symptoms regardless of their previous axis I diagnosis. NF is not a one-size-fits-all type of treatment. Each treatment protocol must be personalized to each patient. With the growing importance of personalized medicine, these types of treatments may become more common in the future.

In this study, QEEG was able to reveal the impairment of these subjects' brain function, as a biomarker, whereas a standard clinical psychiatric interview could not have, especially in the case of the subject that was found to have nothing wrong with him. This may be due to the lack of sensitivity of rating scales and clinical interviews as seen in the study by Boake et al.[103]

One limitation of this study is the lack of data on whether NF produced any positive effects on the cognitive functions in this group. Although the TOVA shows an across the board improvement in performance, hinting that NF has an effect on attention, a more systematic investigation into NF's effects on the cognitive functions in this population with the addition of neurocognitive measures is warranted. Another limitation of this study is that it did not have a control group, and it was not blinded. Finally, other noncontributing factors, such as the prolonged subject therapist interaction, and the heterogeneity of the subject population could not be assessed and ruled out. However, it is the goal of this study to foster better designed studies in order to assess the efficacy of NF in this patient population.

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Author Contributions

TS contributed to conception, contributed to acquisition and interpretation, drafted manuscript, critically revised manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy. EE contributed to conception, contributed to analysis and interpretation, drafted manuscript, critically revised manuscript, agrees to be accountable for all aspects of work ensuring integrity and accuracy. IM contributed to interpretation. HK contributed to acquisition. GO contributed to acquisition and analysis. OS contributed to analysis.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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