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Abstract

Schizophrenia is sometimes considered one of the most devastating of mental illnesses because its onset is early in a patient's life and its symptoms can be destructive to the patient, the family, and friends. Schizophrenia affects 1 in 100 people at some point during their lives, and while there is no cure, it is treatable with antipsychotic medications. According to the Clinical Antipsychotic Trials for Interventions Effectiveness (CATIE), about 74% of the patients who have discontinued the first medication prescribed within a year will have a relapse afterward. This shows an enormous need for developing better treatment methods and better ways to manage the disease, since current therapies do not have sufficient impact on negative symptoms, cognitive dysfunction, and compliance to treatment. In this clinical case series, we investigate the efficacy of quantitative electroencephalography (qEEG)-guided neurofeedback (NF) treatment in this population, and whether this method has an effect on concurrent medical treatment and on the patients. Fifty-one participants (25 males and 26 females) ranging from 17 to 54 years of age (mean: 28.82 years and SD: 7.94 years) were included. Signed consent form was received from all the patients. Most of the participants were previously diagnosed with chronic schizophrenia, and their symptoms did not improve with medication. All 51 patients were evaluated using qEEG, which was recorded at baseline and following treatment. Before recording the qEEG, participants were washed out for up to 7 half-lives of the medication. After Food and Drug Administration (FDA)-approved Nx-Link Neurometric analysis, qEEGs suggested a diagnosis of chronic schizophrenia for all participants. This was consistent with the clinical judgment of the authors. The participants' symptoms were assessed by means of the Positive and Negative Syndrome Scale (PANSS). Besides the PANSS, 33 out of 51 participants were also evaluated by the Minnesota Multiphasic Personality Inventory (MMPI) and the Test of Variables of Attention (TOVA), both at baseline and following treatment. Each participant was prescribed an NF treatment protocol based on the results of their qEEG neurometric analysis. Each session was 60 minutes in duration, with 1 to 2 sessions per day. When 2 sessions were administered during a single day, a 30-minute rest was given between the sessions. Changes in the PANSS, MMPI, and TOVA were analyzed to evaluate the effectiveness of NF treatment. The mean number of sessions completed by the participants was 58.5 sessions within 24 to 91 days. Three dropped out of treatment between 30 and 40 sessions of NF, and one did not show any response. Of the remaining 48 participants 47 showed clinical improvement after NF treatment, based on changes in their PANSS scores. The participants who were able to take the MMPI and the TOVA showed significant improvements in these measures as well. Forty were followed up for more than 22 months, 2 for 1 year, 1 for 9 months, and 3 for between 1 and 3 months after completion of NF. Overall NF was shown to be effective. This study provides the first evidence for positive effects of NF in schizophrenia.

Keywords

biofeedback, electroencephalography, neurofeedback, neurometric analysis, schizophrenia

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Introduction

Schizophrenia is a devastating mental illness that negatively affects the health and well-being of the patients, their families, and the resources of society. For the patient, it most often leads to continued disability and a poor quality of life. The course can be summarized as follows: about 45% recover after 1 or more episodes, about 20% show unremitting symptoms and increasing disability, and about 35% show a mixed pattern with varying degrees of remission and exacerbations of different length.¹

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The preferred treatment for schizophrenia is antipsychotic medication. However, antipsychotic medications target symptoms, have side-effects when used long term, and are not always effective. According to CATIE, about 74% of the patients who discontinued the first medication will have a relapse within a year.² Another problem with antipsychotic treatment is that it does not treat negative symptoms effectively. Antipsychotic medication response is often defined as a 20% reduction in Positive and Negative Syndrome Scale (PANSS) scores; however, this is difficult to translate into the real-world clinical setting.³ In real-life clinical practice, antidepressants, have a success rate of only 40% to 50%. However, with quantitative electroencephalography (qEEG)-guided NF which customizes the treatment to the individual, this may increase to 80% to 90%.⁴

Patients with schizophrenia do not always comply with treatment, and side effects make it hard to stay on them for a prolonged period of time. There is a great need for better treatments and methods to manage the disease.

EEG/qEEG in Schizophrenia

Evaluation of EEG and qEEG literature on schizophrenia is complicated by heterogeneity of the illness and diversity of medication and dosage levels. In spite of these differences, considerable agreement nonetheless appears. Abnormal EEG findings are seen in 20% to 60% of patients.⁵⁻⁷ Most often EEGs have been characterized by decreased alpha activity and/or increased beta activity.^{6,8-16} Others have reported shifted alpha mean frequency or reduced alpha responsiveness^{6,9,17} and increased slow activities.^{14,18-21} Negative symptoms have been correlated with delta waves, especially in temporal areas,²² coupled with decreased alpha and increased beta. In studies conducted by John et al 5 subtypes were detected by cluster analysis. qEEG profiles were characterized by increased theta and decreased alpha and beta in anterior regions; excessive beta in anterotemporal regions; increased theta and alpha with decreased beta; increased alpha with a decrease in all other activities especially delta; and theta in frontal areas, and excessive theta and delta in posterior areas.²³ Groups identified by this cluster analysis have displayed different responses to treatment with haloperidol²⁴ or risperidone.²⁵ Additional evidence of heterogeneity has been provided in qEEG studies by other groups.^{26,27} Other studies have shown greater coherence in patients compared to healthy controls.^{28,29}

Antipsychotic medications, especially neuroleptics, tend to normalize qEEG deviations (ie, increase alpha power and reduce beta power).^{21,30,31} Medication was associated with clinical improvement and increases in spectral power but not with changes in coherence values. This confirms earlier investigations, suggesting that increased coherence reflects the presence of anomalous cortical organization rather than medication effects or transient states related to acute clinical disturbance.^{32,33}

Other studies have shown that neuroleptics increase slow activity and decrease beta activity.³⁴⁻³⁶ However, there are reports of increased delta in patients off medication for several weeks^{11,14,37} and reduction in delta or theta when medication

is resumed.^{30,38,39} The decrease in alpha power was associated with patient's psychotic symptoms^{40,41} and clinical improvement in negative symptoms following clozapine treatment was correlated with the degree of photically driven alpha EEG normalization in the frontal cortex.^{42,43}

NF in Schizophrenia

NF is an operant conditioning paradigm whereby patients are given contingent audio/visual rewards for producing specific patterns of brain wave activity. Since the 1960s, studies have shown that through NF patients can be taught to promote normal functioning of the brain by normalizing dysfunctional brainwave patterns characterized by excessive slow wave activity.^{44,45} NF presents the user with real-time feedback on brain wave activity, typically in the form of a video display and sound. The aim is to provide real-time information to the Central Nervous System (CNS) as to its current activity. For instance, people are asked to increase beta or sensorimotor rhythm (SMR) and decrease delta and theta. When the desired paradigm is accomplished, the patient is rewarded with a moving display and/or a sound. This is operant conditioning. In this study, the participant had to keep an airplane on the monitor above or below a set threshold. When the condition was not met, the tone stopped. Rewards included the receipt of points. Manual threshold setting was used since auto thresholding made the threshold too easy to reach, and no learning takes place.

Eric Kandel won a Nobel Prize in 2000 for showing that synaptic mechanisms of classical conditioning and operant conditioning (including RNA/DNA mechanisms) are universal throughout the animal kingdom, including humans. There is sensitization and habituation which are also scientifically understood but are not generally effective or long lasting and do not involve the same plasticity mechanism as operant and classical conditioning.⁴⁶

NF can help attention-deficit hyperactivity disorder (ADHD) and social skills of children with ADHD,⁴⁷⁻⁴⁹ seizure disorder,⁵⁰ learning disabilities (LD),⁵¹⁻⁵⁴ substance abuse,⁵⁵⁻⁵⁷ depression,⁵⁸⁻⁶¹ personality and mood instability,^{62,63} and in significantly improving or redressing the symptoms of post-concussion syndrome (PCS),⁶⁴⁻⁶⁸ as well as improving similar symptoms in non-PCS patients.⁶⁸

In a study of slow cortical potentials, NF showed an increase in cognitive functions in patients with schizophrenia.⁶⁹⁻⁷¹ Another controlled case study showed the benefit of NF for sleep problems in chronic schizophrenia.⁷² Of 150 schizophrenic patients, 143 were discharged after self-regulation galvanic skin resistance (GSR) training. This group had an average hospitalization of 9 years (maximum 45 years). After the biofeedback (BF) treatment, they remained out of hospital for of 3 years.⁷³ There are reports of successful stress reduction with EMG BF in patients with schizophrenia.^{74,75} Although these were BF paradigms and not NF, they demonstrate the feasibility of operant conditioning with schizophrenia.⁷⁰

Current available evidence does not provide enough information to predict which antipsychotic will provide the best treatment with the least side effects. Therefore, current drug

selection involves a trial and error approach.⁷¹ One-size-fits-all treatment may not be beneficial and more personalized treatments may be more helpful. Using low-frequency (1 Hz) stimulation with repetitive transcranial magnetic stimulation (rTMS) over the left temporal-parietal cortex, Hoffman et al,⁷⁶ found statistically significant decreases in auditory hallucinations in schizophrenia as compared with sham stimulation. These results have been replicated by d'Alfonso et al.⁷⁷ Rollnik et al⁷⁸ used fast rTMS of 20 Hz at 80% motor threshold in schizophrenia, and found that 2 weeks of daily treatment over the left dorsolateral prefrontal cortex significantly reduced psychotic symptoms, whereas depressive and anxiety symptoms did not change. These rTMS studies raise the possibility that NF could be an alternative treatment for depression⁷⁹ and schizophrenia.

While NF has been extensively studied in the treatment of many disorders, there have been no published reports on its clinical effects in the treatment of schizophrenia besides its utility in sleep.

Materials and Methods

The study included 51 participants (mean age 28.8 ± 7.9 years) of whom 25 were male (mean age 27.8 ± 5.8 years) and 26 were female (mean age 29.8 ± 9.6 years). Education levels were: 1 elementary school graduate, 4 middle school graduates, 2 middle school dropouts, 17 high school graduates, 1 attending high school, 1 high school dropout, 15 university graduates, 8 attending university, and 2 university dropouts. The average age of onset of the illness was 20.5 years (± 6.7 years), and the average duration of the illness was 8.8 years (± 6.9 years). Of the 51 participants, 24 had a family history of schizophrenia. All used medication prior to the treatment. The mean of the total number of medications in the past was 3.4 (± 2.1), and currently was 1.6 (± 1.6). Eight of the 51 had been hospitalized previously, and all had been treated as outpatients.

All patients met *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition [DSM-IV]) guidelines for schizophrenia, had received at least 1 ineffective treatment and had a total PANSS score of 70 or above. Additionally, the participants had no physical illness and laboratory tests (hemogram, B12, B6, folic acid, thyroid stimulating hormone (TSH), and urine drug screening for illicit drugs) were normal. Finally, the baseline NxLink Database classification showed similarity with the schizophrenia discriminant at the $P < .01$ level or better, confirmed with the clinical judgment of the first author. Subjects with a comorbid psychiatric disorder, a history of past or present drug abuse, a head trauma with loss of consciousness, a risk of suicide and/or abnormal blood test results were excluded from the study.

PANSS, MMPI and TOVA were administered to all participants. Data were not obtained from those whose cognitive state invalidated the results. PANSS was obtained from all 51 participants, and MMPI and TOVA from 33 participants.

To ensure that the baseline EEG was not contaminated by any medication, all participants were washed out for 7 half-lives of the medications (eg, if they were on risperidone, the 7 half-life of the medication is 6 days, so qEEG was recorded

on the seventh day). qEEGs were recorded with a FDA approved Lexicor Neurosearch-24 qEEG system (software version 3.10). Samples, at 128 samples per second, were analyzed using the FDA approved Nx-Link database software (version 2.40). This neurometric approach is based on quantitative measurements of electrophysiological data which reflect various aspect of brain function and is based on the work of John et al. It provides a precise, reproducible estimate of the deviation of an individual record from normal.⁸⁰ EEGs were compared with the NxLink database before and after treatment, as well as after every 20 sessions. Divergence of electrical activity from norms, guided NF training of the areas that showed deviations from normal. In neurometric qEEG analysis, variables are Z scores (distance from the norm in standard deviation (SD) units. The rationale was that the participants who normalized their qEEG Z scores would benefit the most. After the qEEG, and only if necessary to avoid a full-blown psychotic episode, medication was reintroduced. Otherwise, the participants remained medication free. Antipsychotic medications could not then affect the EEG, especially by increasing coherence and coherence abnormalities. All the NF training was by Lexicor Biolex software. The mean number of sessions was 58.5 within 24 days to 91 days. Each session was 60 minutes long (30-minute rest between 30 minutes of training).

Electrode sites were based on the qEEG location of the deviant Z scores. A general rule is to link the patient's symptoms to deviant Z scores located in regions of the scalp related to functional specialization in the brain.⁶⁵ The electrode sites for training were based on the International 10-20 system except for FPO₂ site.⁸¹

Because of the lack of publications in the area of NF treatment in schizophrenia, we have relied on our clinical experience in determining the brain areas to be treated. We first treated hypercoherence, and then concentrated on areas that showed increased relative power. This was done for all brain areas. The list given below is a general summary of training protocols used.

Hypercoherence can be considered as a lack of differentiation of brain functions or as a decrease in "flexibility" of functioning.

FP1-FP2, F3-F4: Alpha coherence inhibit, alpha inhibit, beta (21-32) inhibit;

C3-C4, P3-P4, T3-T4: Beta coherence inhibit, beta (13-32) inhibit, delta inhibit;

O1-O2: Theta coherence inhibit, theta inhibit, beta (13-32) inhibit.

Based on qEEG analysis

Pz: Inhibit alpha, theta, and beta monopolar montage;

O1: Inhibit alpha and theta monopolar montage.

The frontal and frontotemporal electrode sites below were selected according to the participants' qEEG. Brodmann Area 10 is consistent with the previous schizophrenia research, which implicates this area in deficits of working memory, executive functioning, emotional regulation, and underlying biological abnormalities in synaptic (glutamatergic) transmission.⁸²

Sites which are helpful in attention, motivation, and inhibition of emotions, are:

Fp1-Fp2: inhibit beta, delta, and theta bipolar montage.

In Brodmann area 46 (F3-F4), in a study conducted by Keriakous et al,⁸³ genes that are expressed differently in schizophrenics have been identified. The changes in the gene expression may be related to the changes in the symptom profile of progressing schizophrenia in some patients.⁸³

This site has been found to be helpful in judgment, plan, sustain attention, working memory, inhibition of responses, and verbal episodic memory retrieval:

F3-F4: inhibit alpha coherence, alpha, and beta bipolar montage.

Neurobiological and behavioral data are beginning to show that a common element in schizophrenia is the dysregulation of emotional arousal (eg, the hyperarousal associated with paranoid symptoms),⁸⁴ hypoarousal associated with negative symptoms,⁴¹ and cognitive deficits secondary to both hyper- and hypoarousal.⁸⁵ Although a large body of publications suggests a prefrontal deficit in schizophrenia, newer findings suggest an imbalance, or dysregulation between the 2 primary components of a prefrontal–limbic negative feedback loop.^{86,87} This can be related to the excitatory component of the amygdala,^{88,89} and the inhibitory component provided primarily by the prefrontal regions.^{90,91}

The right frontal pole orbital (FPO₂) site is helpful in fear and anxiety problems. This site is off the standard 10-20 system and sits at the juncture of the right brow bone and the top of the nose, in the inner corner of the eye socket.⁸¹

FPO₂: reward alpha or theta; inhibit theta or alpha monopolar montage.

The sensory area is usually used for its calming effect:

Cz-C4: reward SMR up; inhibit alpha and theta bipolar montage and helpful in sleep;

Cz-C4: inhibit delta and theta bipolar montage.

Paranoid schizophrenia tends to show differences in BA10 and 46 and the prefrontal–limbic circuit.^{82,83} The corresponding NF training lead was found to be helpful in paranoia:

F7-T3: inhibit alpha, theta, and beta bipolar montage.

The following sites may be helpful for auditory hallucinations. Functional magnetic resonance imaging showed that this group shows significantly lower connectivity between left temporal cortex and left dorsolateral prefrontal cortex.^{92,93}

F7-T3, T3-T4: inhibit alpha and theta bipolar montage.

This site below may be helpful for visual hallucinations (VHs).

O1-O2, P3-P4: inhibit theta and delta.

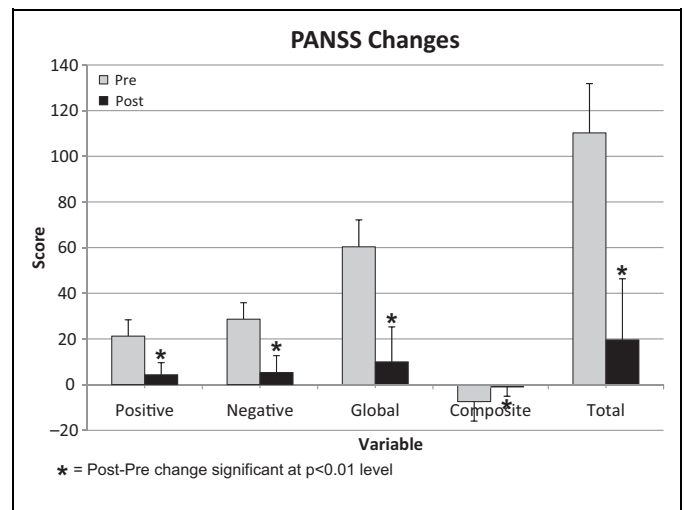


Figure 1. Positive and Negative Syndrome Scale (PANSS) changes.

The criteria used to shift from one site to another were the Z score values of the qEEG, complemented by the first author's clinical experience.

Results

Of the 48 participants, 47 showed clinical improvement after NF treatment, based on PANSS scores. The participants who were able to take the MMPI and the TOVA showed significant improvements on these measures as well. Of the 51 patients, 3 dropped out of treatment between 20 and 40 sessions of NF treatment and 1 out of 51 did not show any response. Forty of the participants in this study were followed up for more than 22 months, 2 were followed for 1 year, 1 was followed for 9 months, and 3 were followed for between 1 and 3 months after the completion of their NF treatment. The mean number of sessions completed by the participants was 58.5 sessions within 24 days to 91 days.

Based on the PANSS, the group, as a whole, showed a statistically significant improvement. At baseline the PANSS total score (mean ± SD) was 110.24 ± 21.62 (positive: 20.22 ± 7.22 ; negative: 28.66 ± 7.22 ; and global: 60.36 ± 11.77) (Figure 1 and Table 1). Posttreatment, the PANSS total score was reduced to 19.56 ± 26.78 (positive: 4.30 ± 5.30 ; negative: 5.30 ± 7.38 ; and global: 9.96 ± 15.32). The total change in the PANSS total score was -90.7 (positive: -16.9 ; negative: -23.4 ; and global: -50.4) which was significant at the $P < .01$ level based on a repeated measures analysis of variance (ANOVA), with accounting for intraparticipant effects ($F_{1,100} = 370.61$, $\eta^2(1,100) = .88$). Overall, the mean percentage change observed in this group was $82\% (\pm 23\%)$.

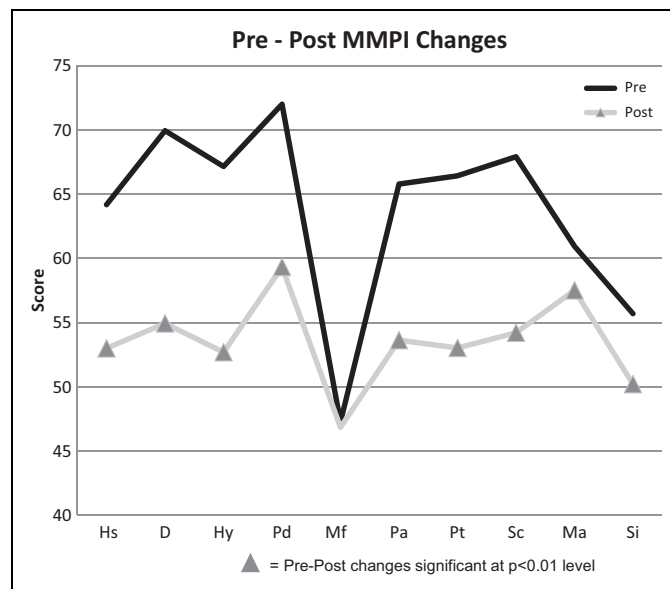
Based on the PANSS, 47 of the 48 patients responded to treatment, as defined by a 20% or higher decrease in the total score, the criteria used in clinical trials.³ This result was in agreement with clinical observations. All participants tolerated, and were compliant with, the treatment.

Table 1. Changes in the Severity of Illness Based on the Positive and Negative Syndrome Scale (PANSS)

Score	Positive		Negative		Global		Composite		Total	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Mean	21.22	4.30	28.66	5.30	60.36	9.96	-7.44	-1.00	110.24	19.56
Std. Dev.	7.17	5.30	7.22	7.38	11.77	15.32	8.50	4.07	21.62	26.78
Change	-16.92		-23.36		-50.40		6.44		-90.68	
$F_{1,102}$	251.97		275.34		340.27		24.45		370.61	
$\eta^2(1,102)$.84		.85		.87		.33		.88	
Significance	$P < .01$		$P < .01$		$P < .01$		$P < .01$		$P < .01$	

Table 2. Changes in the Severity of Illness Based on the Minnesota Multiphasic Personality Inventory (MMPI)

Score	Schizophrenia		Paranoia		Psychopathic Deviation		Depression	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Mean	67.91	54.21	65.79	53.64	72.00	59.33	69.94	54.94
Std. Dev.	15.00	10.06	13.49	6.87	14.22	12.99	14.31	13.67
Change	-13.70		-12.15		-12.67		-15.00	
$F_{1,64}$	25.77		25.37		26.01		20.74	
$\eta^2(1,64)$.43		.44		.45		.39	
Significance	$P < .01$		$P < .01$		$P < .01$		$P < .01$	

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

MMPI was administered before and after treatment; however, results were only available for 33 out of the 51 participants. Four scores were analyzed (Table 2 and Figure 2); schizophrenia, paranoia, psychopathic deviation, and depression (Figure 2).

There was a trend toward normalization in all the MMPI. Changes were statistically significant (except for masculinity/

femininity and mania scores) based on a repeated measures ANOVA, taking into account intraparticipant interactions.

TOVA was conducted at baseline and after treatment. Previous experience with this test shows that patients with schizophrenia have a tendency to perform poorly on the auditory portion of the test.⁹⁴ Tables 3 and 4 and Figures 3 and 4 show it was true for this group of patients. There is a difference both with the norms and between the visual and auditory *T*-scores for this group. Data were available for only 34 participants since, due to their symptomatology at baseline, not all participants were capable of taking this test.

In general NF normalizes the *T* scores. As expected, the auditory scores are lower (less normal) than the visual scores. Although all scores showed improvement, in the visual subtest only Omission Errors and Reaction Time Variability shows statistically significant improvement. In the auditory subtest, all scores shows statistically significant increases (albeit the Reaction Time showed significance at a lower level) based on repeated measures ANOVA, accounting for intraparticipant variability.

qEEG results were compared against the NxLink diagnostic database (Table 5).

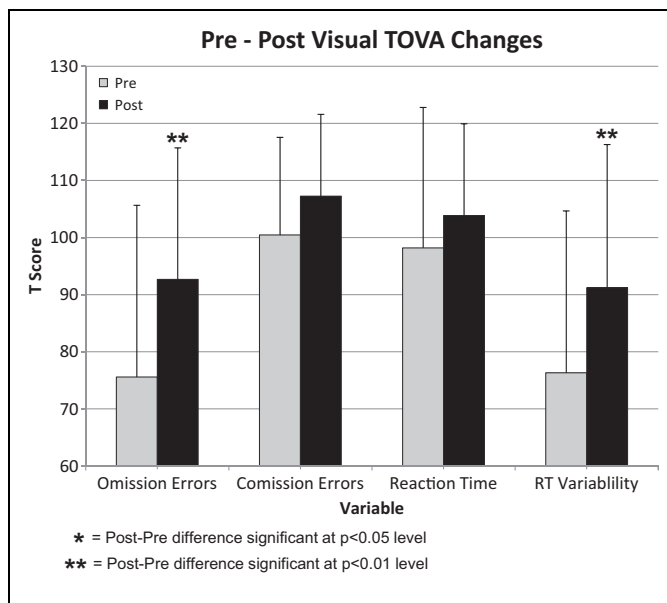
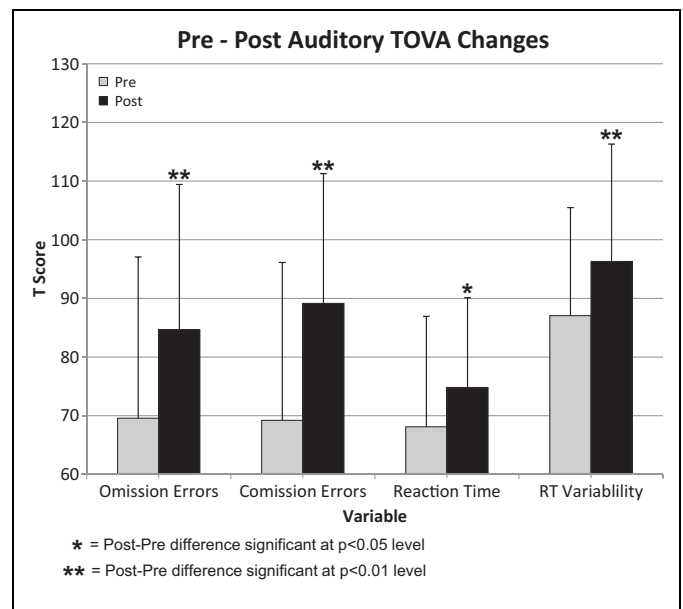
Of the 51 participants, 19 responded to treatment and their brain electrical activity changed to the point where they could no longer be classified as schizophrenic, using the NxLink database ($P < .01$ chi-square). The qEEG of 31 did not change enough to exclude them from a schizophrenic classification, and 1 participant's post EEG could not be recorded. These electrophysiological changes do not indicate that the "clinical" diagnosis of schizophrenia has changed; it only indicates that the brain electrical activity is no longer similar to those of

Table 3. Changes in Test of Variables of Attention (TOVA)

Score	Visual Subtest							
	Omission Errors		Commission Errors		Reaction Time		RT Variability	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Mean	75.58	92.67	100.45	107.24	98.18	103.85	76.30	91.21
SD	30.08	23.04	17.10	14.34	24.61	16.08	28.36	25.09
Change	17.09		6.79		5.67		14.91	
$F_{1,68}$	9.30		2.34		2.98		7.18	
$\eta^2(1,68)$.21		.06		.08		.17	
Significance	$P < .01$		NS		NS		$P < .01$	

Table 4. Changes in Test of Variables of Attention (TOVA)

Score:	Auditory Subtest							
	Omission Errors		Commission Errors		Reaction Time		RT Variability	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Mean	69.58	84.70	69.21	89.15	68.12	74.82	87.06	96.30
Std. Dev.	27.48	24.73	26.92	22.12	18.83	15.31	18.42	20.01
Change	15.12		19.94		6.70		9.24	
$F_{1,68}$	10.09		19.25		4.18		10.43	
$\eta^2(1,68)$.23		.36		.11		.23	
Significance	$P < .01$		$P < .01$		$P < .05$		$P < .01$	

**Figure 3.** Pre-post visual changes.**Figure 4.** Pre-post auditory Test of Variables of Attention (TOVA) changes.

schizophrenics and does not make any inferences to the clinical symptomatology. The qEEG deviations from normal of the pre-study EEG are as follows (Tables 6 and 7).

As can be observed, 73% of the participants show increased alpha and 20% show increased theta activity.

Hypercoherence was seen in 63% of the participants and asymmetry in 43%. At the end of the study, hypercoherence decreased to 58%.

The qEEG of each of the patients was correlated with the schizophrenia subclassifications of John et al.²³ (Table 8).

Table 5. Pre-Post Comparisons of qEEG Classification^a

Pre – Post-qEEG Classification Change	N	%
Pre-schizophrenic, Post not schizophrenic	19	38%
Pre-schizophrenic, Post-schizophrenic	31	62%
Total (1 participant did not have a post recording)	50	100%

Abbreviation: qEEG, quantitative electroencephalograph.

^a Significant at $P < .01$ level based on χ^2 analysis.

Table 6. Characteristics of the Pre-qEEGs in Relative Power

Type of Deviation From Norm	# of Participants	Percent
Significantly increased alpha	14	27%
Increased alpha	23	45%
Increased alpha total	37	73%
Significantly increased theta	9	18%
Increased theta	1	2%
Increased theta total	10	20%
Increased beta/theta	1	2%
Increased alpha/theta	1	2%
Increased beta/alpha	1	2%
Increased coherence only	1	2%
Other total	4	8%
Increased coherence	32	63%
Increased asymmetry	22	43%

Abbreviation: qEEG, quantitative electroencephalograph.

Table 7. Coherence Changes

Pre	%	Post	%
32	63%	22	58%

The majority was in subtype cluster 3 (47%). Nine participants (18%) did not classify with any of the subgroups. However, these 9 subjects' qEEGs were classified as being similar to schizophrenics by the the NxLink Database. Post-treatment, 44% of the participants did not change classification, 20% changed, and 18% did not fit classify any more with any of the subtypes. Of the 9 participants who did not fit any of subtypes at baseline, 3 fitted into one of the groups after treatment (Table 9).

Discussion

Currently the treatment of choice for schizophrenia is antipsychotic medication. However, the effects of these medications are not consistent and the side effects can be severe, especially when used long term. Newer antipsychotics may be helpful in relieving negative symptoms, but their therapeutic effect is still lacking, especially when it comes to symptoms of mood and cognitive impairment. Despite these problems antipsychotics remain the treatment of choice. In the United States alone, newer antipsychotics have a 90% market share.⁹⁵

Table 8. Quantitative EEG Classification With Schizophrenia Subtype Discriminants

Cluster	Pre	%	Post	%
Cluster 1	8	16%	7	14%
Cluster 2	3	6%	4	8%
Cluster 3	22	43%	16	32%
Cluster 4	9	18%	7	14%
Cluster 5	0	0%	1	2%
Not classified	9	18%	15	30%

Abbreviation: EEG, electroencephalograph.

Table 9. Pre-Post Schizophrenia Subtype Changes

Change	N	%
Classified at pre, not classified at post	9	18%
Changed subtype classification	10	20%
No change	22	44%
Not classified pre and post	6	12%
Not classified at pre, classified at post	3	6%

In this study, we explored the utility and efficacy of qEEG-guided NF treatment in schizophrenia. Based on objective clinical measures, NF did have an effect. The PANSS showed a statistically significant improvement in all measures, and the improvement was greater than the 20% seen in most antipsychotic studies. The mean percentage change observed was 82% ($\pm 23\%$). It showed an effect on both positive and negative symptom scores, as well as on the global score. MMPI scores, except for masculinity/femininity and mania (which were not high initially), normalized at a statistically significant level. The depression score was higher than the schizophrenia score, which may lead to the question as to whether these were schizophrenic or depressed patients with schizophrenia-like symptoms. Previous experience with the MMPI shows that the single schizophrenia score is not the highest, and other scores can be higher. In a study conducted by Walters, it was observed that the depression/schizophrenia (schizophrenia/depression) high-point pair was the most frequent finding in a heterogeneous sample of inpatients with schizophrenia.⁹⁶ Electrophysiologically, the NxLink database did not classify the qEEG changes seen in any of the patients as similar to those seen in depression, which is consistent to the findings in other studies.⁹⁷ In a study conducted by Knott et al, the accuracy of separation and the sensitivity/specificity for depression using discriminant functions derived from qEEG was found to be 91.3% (for both), thus showing that electrophysiologically it is possible to distinguish depression from other diagnostic categories at a high level of accuracy and specificity.⁹⁸ Another factor that may contribute to the high depression score may be that these participants, due to the nature of their illness, feel depressed (although they may not meet the criteria of a major depression diagnosis), and therefore rate the MMPI accordingly. Finally, since all of the patients were subjected to a rigorous clinical interview by the first author,

Table 10. Number of Treatment Drugs Needed Before and After NF Treatment

Number of Treatment Drugs	Pre	Post
Mean number of drugs	1.1	0.7
Standard deviation	1.15	0.9
0 Drugs	20	27
1 Drug	15	14
2 Drugs	9	8
3 or More drugs	7	2

Abbreviation: NF, neurofeedback.

none of them was found to meet the criteria for an affective disorder, whereas all of them met the *DSM-IV* criteria of schizophrenia.

When the baseline qEEG results were analyzed, the NxLink database was able to classify all of the patients as having a brain electrical activity similar to chronic schizophrenics. After treatment, 19 participants' brain electrical activity could no longer be classified as being similar to chronic schizophrenics.

Although it can be concluded that NF treatment was effective, it is important to translate these changes into how the treatment affected the quality of life. The participants were followed up for an average of 2 years after the completion of their NF. The observations are presented here to add a human component to the study:

Twenty-seven participants did not need any medication, and one was able to complete medical school. In schizophrenia, noncompliance is quite high and 74% discontinue their first medication. NF was an effective treatment; and since none of these patients needed medication, the problem of noncompliance was solved.

The remaining 24 participants required medication. One attempted suicide 6 months after NF while he was on medication. His rationale was that if he could not be cured there was no point in living. Fortunately, he did not succeed. One participant's mother called our center periodically over a span of 4 years relaying a variety of minor somatic complaints by her son, such as "There's a pain in my heart." These were managed easily by adjusting the participant's medication. One female patient remained medication free for 1 year, until she experienced a mild psychosis. She was put back on 5 mg olanzapine and a second course of NF treatment was prescribed. The patient responded very well to treatment and was able to graduate from college. One male participant called our center complaining that his mild paranoia bothered him and that he was having concentration problems at work. However, he was still able to go to work and function at a high level. Another male participant decided to stop taking medication after 2 years and experienced a mild psychosis. He was put back on medication (low dose of Zyprexa 10 mg 1 × 1) and has been stable since that time.

Twelve (12) participants were put back on only 1 medication, and at half the recommended dose. For 6-36 months they did they not experience any side effects such as restlessness, sleepiness, tiredness, and EPS, and they are enjoying an improved, independent life.

Most of the participants developed enough insight to continue medication and keep their follow-up appointments. Overall, compliance (68%) was very good in this group.

At admission, most of the participants and their parents complained about the sedative side effects of medications but after NF these complaints ceased. When followed up (mean: 24 m \pm 19 STD), 27 (53%) participants remained medication free.

Overall all less drugs were required to achieve the same treatment effect. At inclusion, the participants were taking an average of 1.1 medications (\pm 1.2). At the end of treatment, this number was reduced to an average of 0.7 (\pm 0.9) (Table 10). After NF the number of participants not requiring medication increased and the number of drugs needed decreased.

Before treatment, polypharmacy was common and of the 31 patients on medication at the time of admission 52% of the drugs were antipsychotics, 25% were antidepressants, 13% were anticonvulsants, and fewer than 5% were anxiolytics, antiparkinson medications, beta-blockers, lithium and cognitive activators. In this group, multiple antipsychotics, or an antipsychotic with an antidepressant and an anticonvulsant, were common. After NF, for the 24 patients who needed medication 91% were treated with a single antipsychotic. One patient was prescribed an additional cognitive activator, and 2 patients were given an anticonvulsant.

Overall compliance, whether to NF or medication was quite good. Most of the participants developed insight which enabled them to comply with treatment, self-monitor, and most importantly seek help when their condition worsened. Therapeutic compliance is important, but there are a variety of reasons why people discontinue medications: side effects often contribute, along with a lack of insight and cognitive dysfunction; therefore, adding NF treatment to evidence-based medication treatment seems to improve therapeutic compliance. An interesting feature was the prevalence of hypercoherence (63% of the participants, Table 7). A well-functioning brain is differentiated, and each area does its work. From an electrophysiological point of view, electrodes placed close to each other should be coherent, whereas electrodes farther apart are less so.⁶⁵ It may be that the normal differentiation of the brain has been compromised by a disease process whereby the whole brain's network is working in tandem with the illness, thus losing its differentiation and, electrophysiologically, this is manifested as hypercoherence.^{99,100} When this coherence is reduced by NF, the brain is able to conduct its normal operations. Finally, reduced sedation and stabilization with a single antipsychotic at half the therapeutic dose may show that NF prepares brain for the antipsychotics, potentiating their effects.

Dr Andrew Abarbanel, in discussing how NF is useful in ADHD stated that neural networks controlling the attention processes could be adjusted by neuromodulation, and in the long term could be stabilized into a stable state, and that this process yields longer lasting results compared to pharmacological treatment. He further postulated that this form of neuromodulation would be useful in depression, obsessive compulsive disorder (OCD), and schizophrenia, since different

behavior processes are controlled by similar neuropsychological mechanisms which can be self-modulated.¹⁰¹ In a study of OCD, we found NF to be effective, where 33 (92%) out of 36 patients showed improvements in the Yale Brown Obsessive-compulsive Scale and 19 of them (57%) remained symptom free after 2-year follow-up.¹⁰² In another real-time functional magnetic resonance imaging study (rtfMRI) conducted by Ruiz et al 9 schizophrenic patients were able to train the self activation of the right insula, resulting in improved performance on a face recognition task.¹⁰³

Finally, NF is not a one-size-fits-all treatment. Each treatment must be personalized to each patient, and regularly monitored and adjusted for optimum treatment effect. With the growing importance of personalized medicine, these types of treatments may become more common in the future. This issue has recently been addressed by the Report of the National Advisory Mental Health Council's Workgroup in its August 2010 report. According to the report, its definition of personalized is as follows:

"Personalized" means that there is something known about the individual that differentially predicts how he or she will respond to a given treatment. Evidence-based treatment algorithms are helpful, but too general, with little tailoring based on individual differences (eg, genomic variations), and supported by very little actual evidence beyond acute treatment".¹⁰⁴

qEEG-guided NF fits this description since the NF is tailored to the individual qEEG results of the patient.

One area which we will be investigating in a follow-up analysis of the data is the role of the schizophrenia subtype cluster correlations. The questions that will be explored are the role of the subtype classification in the diagnosis and treatment of the patient. In the original article of John et al²³ on which the classification strategy was based, the author was not able to infer any relationship between initial cluster membership and response to treatment. However, since qEEG-guided NF is tailored to the individual's electrophysiological profile (Z score deviations from normals), by default its different electrophysiological subtypes are treated differently. Our current strategy was to normalize hypercoherent areas in order to foster better differentiation of brain areas.

The goal of this study was to investigate the utility of NF as a treatment for schizophrenia 74% of the patients with schizophrenia do not comply with treatment. In our study not only did all but 3 patients comply with the NF regimen (94%), but of those that needed medication 68% of them complied with their drug treatment when followed up to 2 years. NF may be effective in the long term as well as in the short term. In the CATIE study where \$40 million was spent, the efficacy of the pharmacological treatment on the primary measure, staying in the study until completion, was only 26%.^{2,3}

Although the results were positive, it would be appropriate to investigate whether these results are replicable with better, more controlled study designs. It is our hope that these results will spur research in double-blind controlled trials, since

currently an effective, long-term treatment for this group of patients does not exist.

Declaration of Conflicting Interests

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