Schizophrenia and the Efficacy of qEEG-Guided Neurofeedback Treatment: A Clinical Case Series

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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 afterwards. 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 QEEG Guided Neurofeedback (NF) treatment in this population, and whether this method has an effect on these patients, and its effect on concurrent medical treatment.

Fifty-one subjects (25 males, 26 females) ranging from 17-54 years old (mean: 28.82y, SD: 7.94y) were included. A signed consent form was received from all the patients. Most of the subjects 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 all medications were discontinued and the subjects were washed out for up to 7 half lives of the medication they were on. Recorded QEEGs were analyzed using FDA approved Nx-Link Neurometric analysis, which suggested a diagnosis of chronic schizophrenia for all the subjects tested.

This was consistent with the clinical judgment of the authors. The subjects' symptoms were assessed by means of the Positive and Negative Syndrome Scale (PANSS). Besides the PANSS, 33 out of 51 subjects were also evaluated by the Minnesota Multiphasic Personality Inventory (MMPI) and were administered the Test of Variables of Attention (TOVA), both at baseline and following treatment. Each subject was prescribed a NF treatment protocol based on their QEEG Neurometric analysis results. Each session was 60 minutes in duration, with 1-2 sessions per day where a 30 minute rest was given between sessions, when 2 were administered during the day. Changes in the PANSS, MMPI and TOVA measures were analyzed to evaluate the effectiveness of NF treatment. The mean number of sessions completed by the subjects was 58.5 sessions within 24 days to 91 days.

Forty-seven out of 48 schizophrenic subjects showed clinical improvement after neurofeedback treatment, based on changes in their PANSS scores. The subjects who were able to take the MMPI and the TOVA showed significant improvements on these measures as well. Three out of 51 patients dropped out of treatment between 20 and 40 sessions of NF treatment and 1 out of 51 did not show response. Forty of the subjects 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 completion of their NF treatment. Overall NF treatment was shown to be effective in this group of subjects studied.

This study provides the first evidence for positive effects of neurofeedback treatment on clinical outcome measures in schizophrenia. The results of this study encourage further research. The goal of this study was to foster further controlled studies in this methodology.

INTRODUCTION

Schizophrenia is a devastating mental illness which negatively affects the health and well being of the sufferers, their family and the resources of society. For the sufferer it most often leads to continued disability, and a poor quality of life. Current estimates of the distribution of patients over broad patterns of medium-term course can be summarized as follows: about 45% recover after one 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].

Currently the preferred treatment for schizophrenia is antipsychotic medication. However, antipsychotic medications mainly target the symptoms, have side-effects when used long term, and are not always effective. According to the Clinical Antipsychotic Trials for Interventions Effectiveness (CATIE) about 74 % of the patients who discontinued the first medication prescribed will have a relapse within a year[2]. Another problem with antipsychotic treatment in schizophrenia is that they do not target negative symptoms effectively. In clinical trials, 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 a real life clinical practice,

antidepressants, which are currently prescribed to everyone with the diagnosis of depression, have a success rate of only 40-50%. However, with QEEG guided NF treatment, which in essence customizes the treatment to the individual, this rate may increase to 80-90%[4].

Finally, there is the problem of compliance. Schizophrenics do not always comply with their treatment, and the side effects these medications elicit make it even harder to stay on them for a prolonged period of time. This shows that there is a great need for better treatments and methods to manage the disease.

EEG/QEEG Findings In Schizophrenia

Evaluation of EEG and QEEG literature on schizophrenia is complicated by the evident heterogeneity of the illness and the diversity of medication histories and dosage levels at the time of examination. In spite of these potential sources of difference among findings, considerable agreement nonetheless appears. There have been numerous studies conducted on the EEG and QEEG changes in schizophrenia. Abnormal conventional EEG findings are seen in 20% - 60% of schizophrenic patients[5]. Most often schizophrenic EEGs have also been characterized by decreased alpha activity and/or increased beta activity [5-14]. Others have reported shifted alpha mean frequency or reduced alpha responsiveness[15, 16] and increased slow activities[17-21]. In studies where symptoms were correlated with EEG changes, negative symptoms have been correlated with delta waves especially in temporal areas[22] coupled with the decreased alpha and increased beta activity. Other studies have found heterogeneity in the QEEG findings, and these subgroups had different treatment response characteristics. In studies conducted by John et al. (8) five subtypes were detected by a cluster analysis, with their QEEG profiles characterized by increased theta and decreased alpha and beta in anterior regions; excessive beta especially in anteriotemproal regions; increased theta and alpha with decreased beta; increased alpha with a decrease in all other activities with a noticeable decrease in delta; and theta in frontal areas, and excessive theta with excessive delta in posterior areas[23]. Schizophrenic patients with QEEG profiles corresponding to some of the groups identified by this cluster analysis have been reported to display differential responses to treatment with haloperidol[24] or risperidone[25]. Additional evidence of heterogeneity in the schizophrenic population has been provided in QEEG studies by other groups[26, 27]. Other studies conducted have shown greater values of coherence in schizophrenic patients as compared to healthy controls[28, 29].

The QEEG effects of antipsychotic medications, especially neuroleptics, have been studied in this population. What these findings have in common is that these drugs tend to normalize the QEEG deviations observed in schizophrenics (i.e., increase alpha power and reduce beta power)[30-31]. Medication treatment was associated with clinical improvement and increases in spectral power, but not with changes in coherence values. These results confirm those obtained by earlier investigations and suggest that increased coherence reflects the presence of anomalous cortical organization in schizophrenics rather than medication effects or transient states related to acute clinical disturbance[32].

Other studies have also shown that neuroleptics increase slow activity and decrease beta activity.[33, 34] However, there are reports of increased delta in patients off medication for several weeks[35, 36] and reduction of delta or theta when medication is resumed[37-39]. Studies have also shown that the decrease in alpha power was associated with patient's psychotic symptoms [50, 42] and that the clinical improvement in negative symptoms following clozapine

treatment was correlated with the degree of photically driven alpha EEG normalization in the frontal cortex[42-44].

Neurobiofeedback in Schizophrenia

NF 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 characterized by excessive slow wave activity[45, 46]. NF, also called neurotherapy or EEG biofeedback (EEG BF) is a therapy technique that presents the user with real-time feedback on brainwave activity, as measured by sensors on the scalp, 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. The feedback provided by the computer can be both visual and auditory. For instance people are asked to increase beta or SMR and decrease delta and theta. When the desired paradigm is accomplished by the patient he/she is rewarded. This reward can be in the form of a display that keeps on moving, and/or a sound. This process is called operant conditioning and we do this conditioning every day in our lives. In the software used for the study the display was in the form of an airplane where the subject had to keep the plane above or below a set threshold. When the condition is not met the audio tone that is generated stops. As a reward, when a set number of conditions are met, the subject receives points. Thresholds can be set automatically or manually. In this study manual threshold setting was used since the use of auto thresholding engenders laziness. It makes the threshold too easy to reach, to the point that almost anything is rewarded 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[47].

There is empirical evidence that NF can help brain regulation in Attention Deficit Hyperactivity Disorder(ADHD) and social skills of children with ADHD[48-51], seizure disorder[52], learning disabilities (LD)[53-55], substance abuse[56-58], depression[59-61], personality and mood instability[62-64], and in significantly improving or redressing the symptoms of post-concussion syndrome(PCS)[65-67], as well as improving similar symptoms in non-PCS patients[68].

In a study on slow cortical potentials, NF showed an increase in cognitive functions in schizophrenia patients[69,70]. In another controlled case study which shows the effect of NF treatment for sleep problems in chronic schizophrenia patients[71]. Von Hilsheimer and Quirk restored schizophrenics to normal life in the 60s at the Clark Psychiatric Institute in Queen Street Hospital, in Toronto, Canada. Of 150 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 BF treatment they remained out of hospital for follow-up period of three years[72]. There are reports of successful stress reduction with EMG biofeedback in schizophrenia[73]. Although these were BF paradigms and

not NF, they demonstrate the feasibility of operant conditioning (e.g., NF) with schizophrenia and the path is clear for examining the efficacy of a therapeutic intervention in schizophrenia, and the schizotypal spectrum[74].

Currently the 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 by the clinician[75].

Another issue is that a one size fits all treatment approach (usually with antipsychotic medications) may not be beneficial in this particular patient population, and that more personalized treatments may also be more helpful. Using low frequency (1Hz) stimulation with rTMS over left temporalparietal cortex, Hoffman et al.[76], reported statistically significant decreases in auditory hallucinations in schizophrenia as compared with sham stimulation. These results have also been replicated by d'Alfonso et al.[77] using similar treatment parameters. In contrast to the low frequency approach, Rollink et al.[78] used a fast rate rTMS of 20 Hz at 80% motor threshold in schizophrenia and found that 2 weeks of daily treatment over left dorsolateral prefrontal cortex significantly reduced the psychotic symptoms, whereas depressive and anxiety symptoms did not change significantly. The positive findings in the rTMS studies have raised the possibility that NF, which is a safer way to modulate brain activity, could be an alternative treatment option for depression[79] as well as for 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.

MATERIAL AND METHODS

The study included 51 subjects (mean age 28.8y ±7.9y) of which 25 (mean age 27.8y ±5.8y) were male and 26 were female (mean age 29.8y ±9.6y). The education levels of the subjects were as follows: 1 elementary school graduate, 4 middle school graduates, 2 middle school dropouts, 17 high school graduates, 1 attending high school, 1 high school drop-out, 15 university graduates, 8 attending university, and 2 university drop-outs. The average age of onset of the illness was 20.5 y (±6.7y), and the average duration of the illness was 8.8y (±6.9y) Twenty-four out of 51 had a family history of schizophrenia. All the patients in the study used medication prior to the treatment. The mean of the total number of medications used per subject in the past was 3.4 (± 2.1), and the average number of medications they were currently taking was 1.6 (± 1.6). Eight of the 51 had been hospitalized previously. All of the subjects have been treated as outpatients previously.

All patients were required to meet the DSM-IV guidelines for schizophrenia, should have had received at least one treatment modality which was ineffective, and have a total PANSS score of 70 or above. Additionally, the subjects should not have any history of physical illness and the baseline laboratory tests (Hemogram, B12, B6, Folic Acid, THS and urine drug screening for illicit drugs) had to be normal. Finally the baseline NxLink Database classification needed to show similarity with the schizophrenia discriminant at the $P < 0.01$ level or better confirmed with the clinical judgment of the first author. The presence of any

other psychiatric disorder, history of past or present drug abuse, and head trauma with loss of consciousness, suicide risk and/or abnormal blood test results.

PANSS was administered to all subjects. The MMPI and TOVA tests were also administered to all subjects but data was not obtained from those that due to their cognitive state at pre-treatment could not take these tests or answered in a way that invalidated the results. Of the 51 subjects, MMPI and TOVA data was obtained from 33 subjects.

A pre-treatment medication free QEEG was recorded for each of the 51 subjects. In order to insure that the baseline EEG was not contaminated by any medication, all subjects were washed out for up to 7 half lives of the medications they were taking (for example if they were on Risperidone, the 7 half life of the medication is 6 days, so QEEG was recorded on the 7^{th} day). All QEEGs were recorded with a FDA approved Lexicor Neurosearch-24 qEEG system (software version 3.10). The EEG signals were sampled at 128 samples per second per channel. Samples were analyzed with a normative Neurometric approach using the Nx-Link database software (version 2.40). The Neurometric approach is based on quantitative measurements of salient features extracted from electrophysiological data which reflect various aspect of brain function and is based on the work of E. Roy John. It is a method of quantitative EEG that provides a precise, reproducible estimate of the deviation of an individual record from normal[80]. QEEGs were recorded and 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 is a score equal to the distance (deviation) from the norm in standard deviation units. The rationale behind this approach is that the subjects who normalize their QEEG Z-scores will benefit the most from neurofeedback treatment. After the QEEG, if the subject could not remain medication free, medication was reintroduced. The reason for not administering medication immediately was because antipsychotic medications affect the EEG and especially may increase coherence and coherence abnormalities. However, the guiding criterion for medication administration was to medicate as soon as possible in order to prevent a full-blown psychotic episode. All the NF training was performed using Lexicor Biolex software. The mean number of sessions completed by the subjects is 58.5 sessions within 24 days to 91 days. Each session was 60 minutes in duration where a 30 minute rest between 30 minutes of training.

Electrode sites for training were selected based on the QEEG analysis (using the Nx-Link database). The location of the deviant Z scores is most important no matter what the EEG measure. 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 and the patient's symptoms[81]. The electrode sites for training were based on the international 10-20 system except for FPO_2[82] site.

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. The methodology we found most useful in this group is to first treat any hypercoherence (areas that show increased coherence in comparison to norms) revealed by the analysis of the QEEG recording, and then concentrate on areas that showed increased relative power

activities. This was done in sequence for all brain areas. The list given below is a general summary of training protocols used.

Coherence training was performed according to z-scores. Hypercoherence can be considered as a lack of differentiation of brain functions or as a decrease in "flexibility" of functioning.

FP1-FP2, F3-F4,	α coherence-inhibit, α-inhibit, β(21-32)-inhibit
C3-C4, P3-P4, T3-T4,,	β coherence-inhibit, β(13-32)-inhibit, Delta-inhibit,
O1-O2:	Theta coherence-inhibit, Theta-inhibit, β(13-32)-inhibit

Based on the 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 subjects' QEEG. Brodmann Area 10 is consistent with previous schizophrenia research, which implicates this area in deficits of working memory, executive functioning, emotional regulation and underlying biological abnormalities in synaptic (glutamatergic) transmission[83].

These sites, which are helpful in attention, motivation, and inhibition of emotions, are as follows:

Fp1-Fp2:	inhibit Beta, Delta and Theta	bipolar montage

In Brodmann area 46 (F3-F4), in a study conducted by Keriakous et al.[84],genes have been identified that are expressed differently in schizophrenics. The changes in the gene expression may be related to the changes in the symptom profile of progressing schizophrenia in some patients[84].

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

F3-F4: inhibit Alpha coherence, Alpha, and Beta bipolar montage

Although the signs and symptoms of schizophrenia may be multifaceted neurobiological and behavioral data is beginning to show that a common element in schizophrenia is the dysregulation of emotional arousal (e.g., the hyper-arousal associated with paranoid symptoms)[85], hypo-arousal associated with negative symptoms[86], and cognitive deficits secondary to both hyper and hypo-arousal[87]. Although a large body of publications suggests a prefrontal deficit in schizophrenia, newer findings suggest an imbalance, or dysregulation between the two primary components of a pre-frontal-limbic negative

feedback loop[88, 89]. This can be related to the excitatory component of the amygdala[90, 91], and the inhibitory component provided primarily by the prefrontal regions[92, 93].

The FPO_2 site is helpful in fear and anxiety problems. FPO stands for Frontal Pole Orbital (pre-frontal) and "2" signifies the right side of the brain. This site is off the standard ten-twenty 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[94].

FPO_2: 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[95, 96]. The corresponding NF training lead found to be helpful in paranoia:

F7-T3: inhibit Alpha, Theta and Beta bipolar montage

The following sites below may be helpful for auditory hallucinations. Evidence from fMRI studies conducted also showed that this group shows significantly lower connectivity between left temporal cortex and left dorsolateral prefrontal cortex.[97, 98]

F7-T3, T3-T4: inhibit Alpha and Theta bipolar montage

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

O1-O2, P3-P4: inhibit Theta and Delta

The criteria used to shift from one site to another were the z-score values of the QEEG which was supplanted with the first author's clinical experience.

RESULTS

Forty-seven out of 48 schizophrenic subjects showed clinical improvement after NF treatment, based on changes in their PANSS scores. The subjects who were able to take the MMPI and the TOVA showed significant improvements on these measures as well. Three (3) out of 51 patients dropped out of treatment between 20 and 40 sessions of NF treatment and 1 out of 51 did not show response. Forty of the subjects 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 completion of their NF treatment. The

mean number of sessions completed by the subjects was 58.5 sessions within 24 days to 91 days.

Based on the Positive and Negative Syndrome Scale (PANSS) the group, as a whole, showed a statistically significant improvement. As can be seen in Figure 1 and Table 1, at baseline the Mean PANSS total score was 110.24 ± 21.62 SD (*Positive: 20.22 ± 7.22 SD, Negative: 28.66 ± 7.22 SD, Global: 60.36 ± 11.77 SD*). Post treatment the PANSS total score was reduced to 19.56 ± 26.78 SD (*Positive: 4.30 ± 5.30 SD, Negative: 5.30 ± 7.38 SD, Global: 9.96 ± 15.32 SD*). The total change in the PANSS total score was -90.7 (*Positive: -16.9, Negative: -23.4, Global: -50.4*) which was significant at the $p < 0.01$ level based on a repeated measures ANOVA with accounting for intra-subject effects ($F(1,100) = 370.61$, $\eta^2(1,100) = 0.88$). Overall the mean percent change observed in this group was 82% (± 23% SD).

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	
$\eta^2(1,102)$	0.84		0.85		0.87		0.33		0.88	
Significance	p< 0.01		p< 0.01		p< 0.01		p< 0.01		p< 0.01	

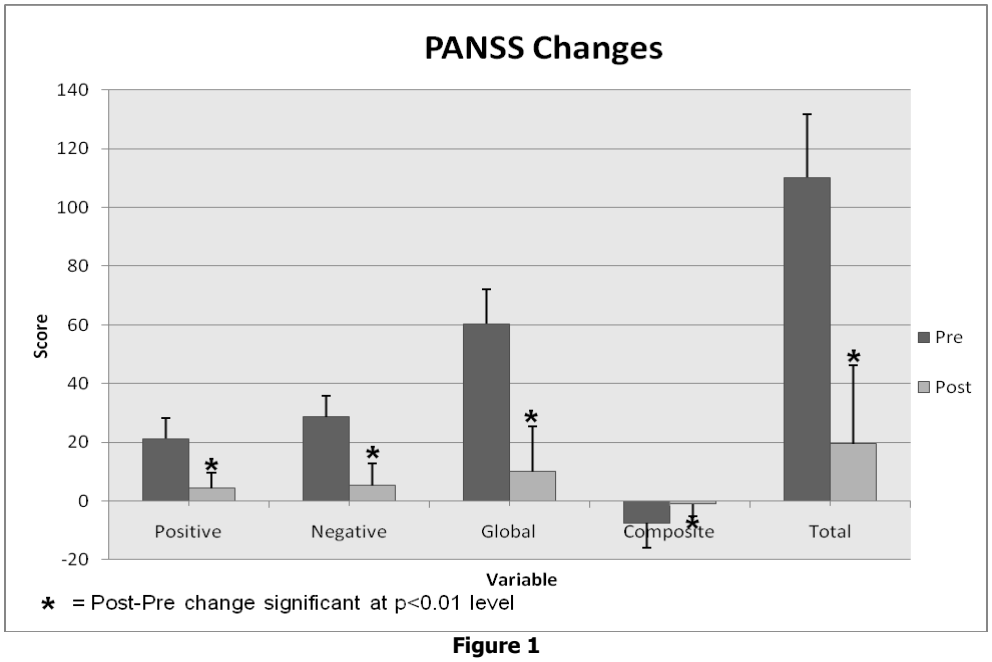

Figure 1

Based on the PANSS results, 47 of the 48 patients who remained in the study responded to treatment as defined by a 20% or higher decrease of the PANSS total score which is the criteria used in clinical trials of antipsychotic medications[3]. This result was in agreement with clinical observations. All subjects tolerated the treatment and complied very well with their session schedules.

An MMPI (the MMPI-2 has still not been validated for a Turkish population) was administered to all subjects before treatment and after completion of treatment, however, results were only available for 33 out of the 51 subjects due to the fact that a baseline MMPI could not be administered and/or was invalid due to some subjects' illness severity. Four scores were analyzed (Table 2, Figure 2). These were the Schizophrenia, Paranoia, Psychopathic Deviation, and Depression Scores. These scores were selected since they target this patient population and the Depression score was analyzed because it showed a high value (70 T-Score). The results of the changes before and after treatment are given in Figure 2 below:

TABLE 2 - Changes In The Severity Of Illness Based On The Minnesota Multiphasic Personality Inventory (MMPI)

	Schizophrenia		Paranoia		Psychopathic Deviation		Depression	
Score:	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	
$\eta^2(1,64)$	0.43		0.44		0.45		0.39	
Significance	$p < 0.01$		$p < 0.01$		$p < 0.01$		$p < 0.01$	

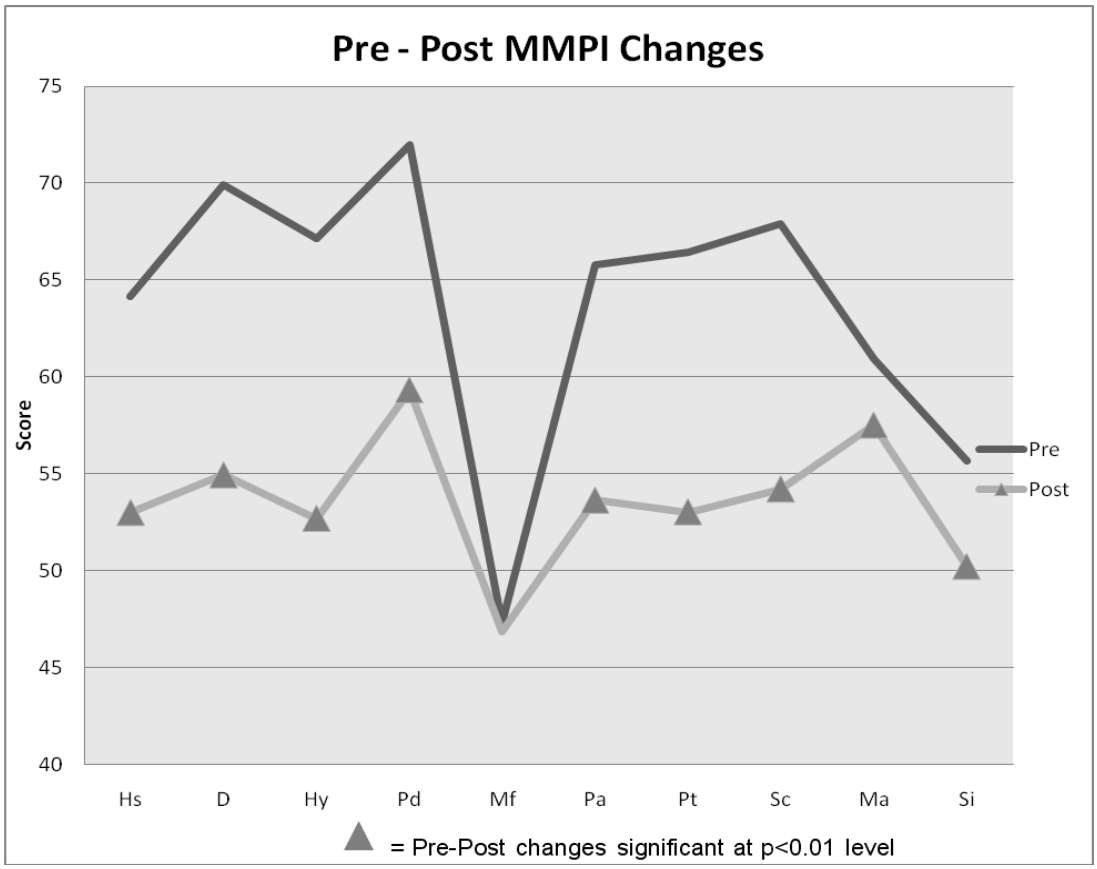

Figure 2

As can be seen there is a trend towards a decrease (normalization) of all the MMPI scores, and the changes are statistically significant (except for Masculinity/Femininity and Mania scores); this is based on a repeated measures ANOVA taking into account intra-subject interactions.

TOVA Results

The Test of Variable of Attention (TOVA) was conducted at baseline and after treatment. Previous experience with this test shows that schizophrenics have a tendency to perform poorly on the auditory portion of the test[99]. As the results given in Tables 3 and 4 and Figures 3 and 4 show, this 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 was available for only 34 subjects since, due to their symptomatology at baseline, not all subjects were capable of taking this test.

TABLE 3 - Changes In Test of Variables of Attention (TOVA)

VISUAL SUBTEST

Score:	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
Std. Dev.	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	
$\eta^2(1,68)$	0.21		0.06		0.08		0.17	
Significance	$p < 0.01$		NS		NS		$p < 0.01$	

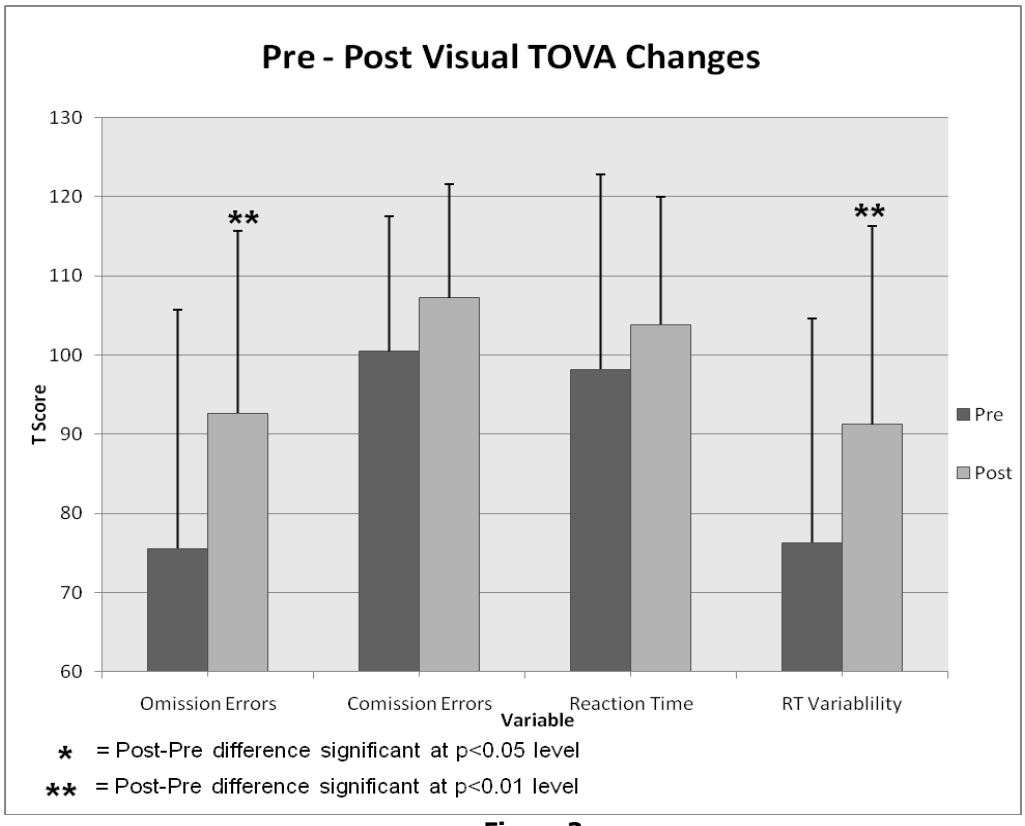

Figure 3

TABLE 4 - Changes In Test of Variables of Attention (TOVA)								
AUDITORY SUBTEST								
Score:	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	
$\eta^2(1,68)$	0.23		0.36		0.11		0.23	
Significance	$p < 0.01$		$p < 0.01$		$p < 0.05$		$p < 0.01$	

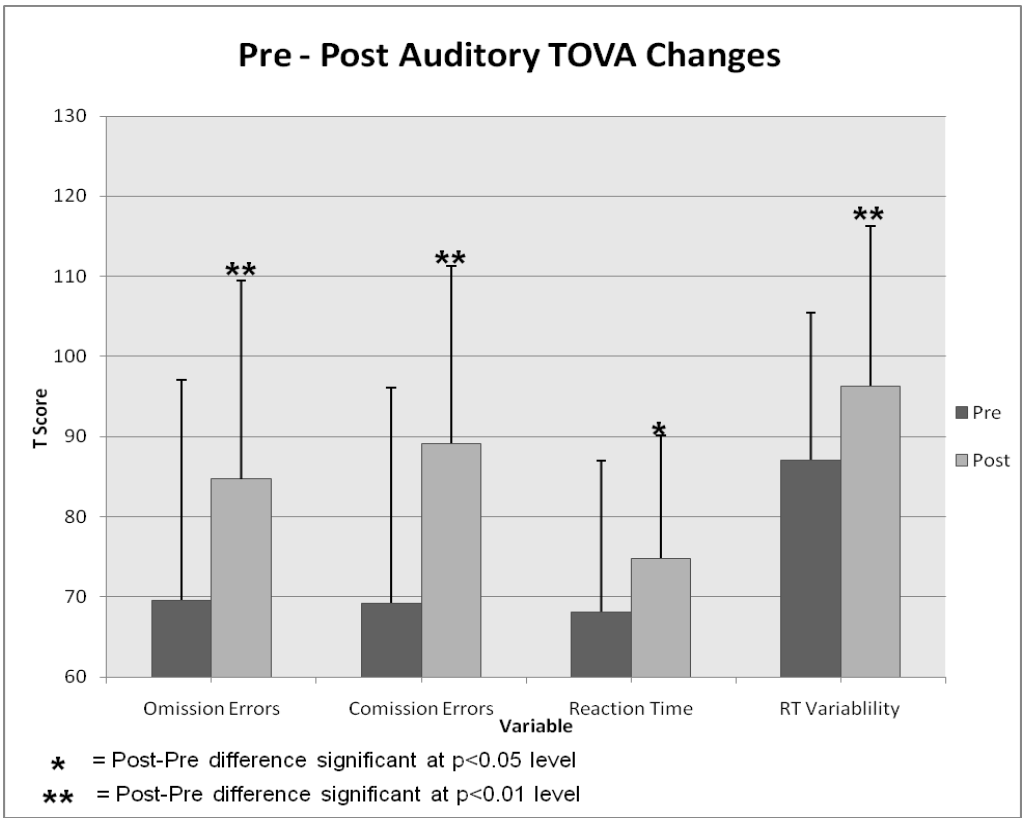

Figure 4

These results show that in general NF treatment increases (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 show statistically significant improvement. In the Auditory Subtest, all scores show statistically significant increases (albeit the Reaction Time showed significance at a lower level) based on repeated measures ANOVA, accounting for intra-subject variability.

QEEG Results

Each subject had a drug free QEEG recorded before treatment and after every completion of 20 sessions. At the end of treatment, a post-treatment QEEG was recorded. All QEEG results were compared against the NxLink diagnostic database. The results are of the correlation with the chronic schizophrenic database are as follows (Table 5).

Table 5 - Pre-Post Comparisons of QEEG Classification		
Pre – Post QEEG Classification Change	N	%
PRE-Schizophrenic, POST-Not Schizophrenic	19	38%
PRE-Schizophrenic, POST-Schizophrenic	31	62%
TOTAL (one subject did not have a post recording)	50	100%

Significant at $p < 0.01$ level based on X^2 analysis

One of the inclusion criteria for the study was for the QEEG to be classified as being similar to the Schizophrenia profile of NxLink data base. Of these 51 subjects, 19 responded to treatment and their brain electrical activity changed to the point where they could no longer be classified as schizophrenic, which was significant at the $p < 0.01$ level (based on chi square statistic). Thirty one (31) subjects' QEEG did not change enough to exclude them from a schizophrenic classification, and one subject'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 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, 7):

Table 6- Characteristics of the PRE QEEGs in relative power		
Type of Deviation From Norm	# of Subjects	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%

Table 7 – Coherence Changes			
Pre	%	Post	%
32	63%	22	58%

As can be observed, 73% of the subjects show increased Alpha activity and 20% show increased Theta activity. Hypercoherence was also seen in 63% of the subjects and asymmetry findings in 43% of the subjects. At the end of the study subjects who showed hypercoherence decreased to 58%.

The QEEG of each of the patients was correlated with the schizophrenia sub-classifications of E. Roy John[23]. The results are given below (Table 8):

Table 8 – QEEG 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%

The majority of the subjects classified as being similar to Subtype Cluster 3 (47%). Nine subjects (18%) did not classify with any of the subgroups (although they did classify as being similar to schizophrenics with the NxLink Database). When the post-treatment EEGs were compared against the schizophrenia subtypes, it was observed that 44% of the subjects did not change their classification, 20% changed their classification, and an almost equal amount (18%) did not classify any more with any of the subtypes after treatment. Of the 9 subjects who were not classified in any of subtypes at the beginning of the study 3 classified into one of the groups after treatment (Table 9).

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%

DISCUSSION

Currently the treatment of choice for schizophrenia is antipsychotic medications. However, the effects of these medications are not consistent and the side effects can be severe, especially when used long term. Newer antipsychotics have been found to be effective in relieving negative symptoms but their therapeutic effect is still lacking, especially when it comes to symptoms of mood and cognitive impairment. The effects of antipsychotics on overall functioning and quality of life as well as their long term efficacy have not been explored in detail either. Despite these problems and the lack of efficacy information, antipsychotics remain the treatment of choice and are widely used in the world. In the United States alone, newer antipsychotics have a 90 percent market share[100].

In this study we attempted to explore the utility and efficacy of QEEG guided Neurofeedback treatment in schizophrenia. Based on objective clinical measures, NF did have an effect in the population studied. As stated above, all PANSS measures showed a statistically significant improvement on all measures, and the improvement was greater than the 20% change seen in most antipsychotic studies. The mean percent change observed in this group was 82% (± 23% SD). It was also able to have an effect on both positive and negative symptom scores, as well as showing an effect on the global score. The MMPI showed similar results where all the scores except for Masculinity/Femininity and Mania

(which were not high to begin with) normalized at a statistically significant level. One question that arises here is why the Depression score is higher than the Schizophrenia score, which may lead to the question as to whether these are schizophrenics or depressed patients with schizophrenic-like symptoms (schizoaffective patients and or subjects with psychotic depression). However, previous experience with the MMPI in a schizophrenic population show that the single Schizophrenia score is not the highest, and other scores can be higher in this group. 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 schizophrenic in-patients[101]. 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[102]. In a study conducted by Knott, Mahoney 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[103] Another factor that may contribute to the high Depression score may be that these subjects, 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, none of them were 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 subjects' brain electrical activity could no longer be classified as being similar to chronic schizophrenics.

Although it can be concluded that NF treatment was effective in this particular group of patients, it is important to be able to translate these changes into how the treatment affected the quality of life of the subjects. The subjects in this study were followed up for an average of 2 years after completion of their NF treatment, and the following observations were recorded. They are presented here to help add a human component to the study:

Twenty seve subjects did not need any medication after the NF treatment. One subject was even able to complete medical school. Since in this group of patients, non-compliance with medication is quite high and 74% discontinue their first medication, NF seems to be (at least in this group) an effective treatment, and since none of the patients needed medication, the problem of non-compliance is addressed with this treatment modality.

The remaining 24 subjects required medication after their NF treatment. The disposition of of them is as follows: One of the subjects attempted suicide 6 months after NF treatment, 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 subject's mother called our center periodically over a span of 4 years relaying a variety of minor somatic complaints her son had, such as "There's a pain in my heart." These were managed easily by adjusting the subject's medication. Otherwise, this subject did not have any other complaints or relapses. One female patient remained medication free for 1 year, until she experienced a mild psychosis. She was put back on 5mg Olanzapine to stabilize her 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 subject 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 subject decided to stop taking medication after 2 years and experienced a mild psychosis. He was put back on medication (low dose of Zyprexa 10mg 1x1) and has been stable since that time.

Twelve (19) subjects were put back on only one treatment medication, and at half the recommended treatment dose, in order to keep them stable. Not only did they not experience any side effects (for a span of 6-36 months) such as restlessness, sleepiness, tiredness and EPS, but they are enjoying an improved and independent life.

Most of the subjects developed enough insight and awareness of their condition to realize that they should not stop taking their medication and keep their follow-up visit appointments. Overall compliance was very good in this group (68%).

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

Overall all less drugs were required to achieve the same treatment effect. At inclusion the subjects were taking and average of 1.1 medications (± 1.2). At the end of treatment this number was reduced to an average 0.7 (± 0.9) drugs. This can also be seen when the number of drugs the subjects were taking was tabulated (Table 10). As can be seen after the completion of the NF treatment, the number of subjects not requiring any medication increased and the number of drugs needed to treat those that needed medication also decreased.

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

When the types of drugs administered before and after treatment were tabulated before treatment polypharmacy was common and of the patients that were on medication at the time of admission (31 patients) 52% of the drugs previously prescribed were antipsychotics, 25% were antidepressants, 13% were anticonvulsants, and fewer than 5% of the drugs were anxiolytics, antiparkinson medications, beta blockers, lithium and cognitive activators. In this group multiple antipsychotics or an antipsychotic with an antidepressant and an anticonvulsant was common. After treatment for those patients that needed medication (24 patients) 91% of them were treated with a single antipsychotic. One patient was prescribed and additional cognitive activator, and 2 patients were given an anticonvulsant.

Some very interesting issues are raised here. Overall compliance, whether to NF treatment or to the treatment medication prescribed after the NF treatment, was quite good. Most of the subjects developed insight into their condition which enabled them to comply with their 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. Another interesting feature in this group was the prevalence (63% of the subjects, see Table 7) of coherence abnormalities (hypercoherence). Normally, a well functioning brain is well differentiated and each area does its work. Looking at this phenomenon from an electrophysiological point of view, electrodes placed close to each other should be coherent, whereas electrodes farther apart are less coherent with each other[81]. It may be that hypercoherence is an indication 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[104, 105]. When this coherence is reduced by NF, the brain is able to conduct its normal operations. Finally, as in the case of reduced sedation complaints and the subjects who were stabilized with a single antipsychotic at half the therapeutic dose, this may show that NF may have an effect of preparing the brain for the antipsychotics and/or potentiating their effects.

In an article by Dr. Andrew Abarbanel regarding how NF is useful in ADHD he stated that neural network 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, OCD and schizophrenia since different behavior processes are controlled by similar neuropsychological mechanisms which can be self modulated[106]. In a study we conducted with OCD patients we found NF to be effective in this group also where 33 out of 36 patients (92%) showed improvement on the Yale Brown Yale–Brown Obsessive-Compulsive Scale[87] and 19 of them (57%) remained symptom free after 2 year follow-up[107].

Finally, NF is not a one size fits all type of treatment. Each treatment protocol 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 (e.g., genomic variations), and supported by very little actual evidence beyond acute treatment[108]. The QEEG guided NF fits the description of personalized since the NF protocol 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 sub-type 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 E. Roy John[23] 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 treatment is tailored to the individual's electrophysiological profile (z-score deviations from normals), by default it 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 neurofeedback as a treatment for schizophrenia. As can be seen, when overall 74% of schizophrenics do not comply with their treatment, in our study using NF treatment, not only did all but 3 patients comply with the NF treatment regimen (94%), but of those that needed medication 68% of them complied with their drug treatment when followed up to 2 years after the cessation of treatment. This shows that NF treatment may be effective in the long term as well as in the short term in a schizophrenic population. 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 and useful to investigate whether these results are replicable with better, more controlled study designs, since in this group of patients we were able to see results comparable to those seen after medication treatment. It is our hope that these results will spur research in better designed, double blind controlled trials, since currently an effective, long term treatment for this group of patients does not yet exist.

DISCLOSURE AND CONFLICT OF INTEREST

Tanju Surmeli, Ayben Ertem, Emin Eralp and Ismet Kos have no conflicts of interest in relation to this article.

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