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High Frequency Prefrontal rTMS for the Negative Symptoms of Schizophrenia: A Case Series

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Abstract

Objectives—The negative symptoms of schizophrenia are difficult to treat and are predictors of poor outcome. New somatic treatments are needed to reverse these symptoms and improve function. One promising approach is repetitive transcranial magnetic stimulation (rTMS), though results to date have been mixed. This pilot study assessed higher doses of rTMS and assessed particular demographic factors that may influence treatment response.

Methods—Five patients with schizophrenia or schizoaffective disorder enrolled to receive 20 sessions of rTMS administered with a Magstim SuperRapid Device at 20 Hz for 2 seconds, ITI 28 seconds, 100% motor threshold (MT) to the left dorsolateral prefrontal cortex (DLPFC) in an open label pilot study. PANSS symptom assessments occurred at two week intervals during treatment and twice at four week intervals after termination.

Results—Treatments were well tolerated with no adverse events. One patient withdrew from the study in the setting of medication non-compliance. Of the patients who completed treatment, two had reductions in positive symptoms by 9% and 26%, maintained at 1 month. A third patient had a 14% reduction in negative symptoms at week 4 and a fourth had a 55% reduction at week 4. Negative symptom improvement was not related to depressive or extrapyramidal symptoms, which were unchanged with treatment.

Conclusions—This pilot study of rTMS treatment for the negative symptoms of schizophrenia is promising with respect to safety and feasibility. The promising preliminary evidence for improvements in this open label setting should be followed up with a randomized clinical trial to establish efficacy. Further work may explore the potential utility of rTMS for the otherwise largely untreatable negative symptoms which account for so much of the morbidity of schizophrenia.

Keywords

transcranial magnetic stimulation; schizophrenia; negative symptoms; prefrontal cortex

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Introduction

Transcranial magnetic stimulation (TMS) is a method of noninvasive electromagnetic neurostimulation that has been studied in the treatment of a range of psychiatric disorders, including affective disorders ([1], [2]), anxiety disorders ([3], [4]) and schizophrenia ([5]). The development of novel neurostimulation treatments may be particularly useful for schizophrenia as many individuals have symptoms resistant to current pharmacotherapies despite growth of options for this illness. In particular, negative symptoms remain refractory to most pharmacotherapy ([6], [7], [8], [9], [10], [11]), which can in some cases worsen them.

Studies suggest repetitive TMS (rTMS) may be useful in the treatment of refractory auditory hallucinations. Applied at low frequency (1 Hz) to the left temporoparietal cortex, it has been shown to reduce the frequency, attentional salience and loudness of auditory hallucinations ([12]; [5]; [13]). These studies are based on the ability of rTMS to decrease cortical excitability ([14]; [15]) and thus reduce regional overactivity associated with auditory hallucinations ([16]). To date, rTMS has been more successful in the treatment of refractory auditory hallucinations (four positive parallel randomized controlled trials out of six total; [12,17–19]) than for negative symptoms (three positive randomized controlled trials [20–22] out of six total [20–25]). In the positive studies, negative symptoms were measured with the Positive and Negative Syndrome Scale (PANSS) with a mean decrease of ten (absolute score; [22]), 30% [21], and 29% [20], all clinically significant. However, optimal TMS dosing has not been established for either symptom cluster. In depression and refractory auditory hallucination (AH) studies, efficacy has been associated with dose ([26–27]). Thus, it makes sense to further explore the potential utility of different doses of rTMS for medication refractory negative symptoms.

Previous randomized sham controlled studies have found high frequency rTMS (e.g. 10–20 Hz) to the left dorsolateral prefrontal cortex (DLPFC) was associated with a subsequent decrease in negative symptoms (e.g. flattened affect, social withdrawal, apathy, poor motivation; ([20–22]). Using a sham-controlled parallel design, two studies found high-frequency (10 Hz) rTMS to the left DLPFC in samples of twenty [22] and twenty-two [20] schizophrenia patients and observed a significant reduction in negative symptoms. In a randomized cross-over trial, Jin et al [21] found that individualized alpha frequency rTMS (compared to 20 Hz) was most efficacious in reducing negative symptoms in a sample of 27 patients. The mechanism for this response may be through increasing cortical excitability in the target region ([21]), as negative symptoms have been shown to correlate with hypoactivity in the dorsolateral prefrontal cortex (DLPFC) ([28]). Furthermore, since rTMS has transsynaptic effects [29], it is possible that deeper targets also associated with negative symptoms (e.g. basal ganglia [30]) might be uniquely targeted with rTMS. In the three negative studies of negative symptoms, although they had similar numbers of patients, the patients differed by being more chronic and having a higher proportion of males [23–25]. Such differences may play a role in predicting response and/or treatment development.

In this case series we explored the safety and feasibility of rTMS for negative symptoms using higher doses than most previous studies (32,000 vs. e.g. 10,000 [22] and 8,000 [31]). Five patients who met DSM-IV criteria for schizophrenia or schizoaffective disorder were enrolled in an open-label trial of high-frequency (20 Hz) rTMS applied to the left DLPFC. Unlike previous studies, these patients were well characterized as to demographics and clinical factors which might influence negative symptom response to rTMS. Outcomes of interest included both negative symptoms and social function, which are often associated in schizophrenia patients.

We hypothesized that patients would demonstrate a significant reduction in negative symptomatology and social deficits following the application of high-frequency rTMS to the left DLPFC.

Materials and Methods

Patients

Patients were recruited from the outpatient clinics of the Washington Heights Community Service and the Lieber Center Clinic at the New York State Psychiatric Institute (NYSPI) and through internet advertisements. Individuals meeting DSM-IV criteria for schizophrenia or schizoaffective disorder as assessed by the Diagnostic Interview for Genetic Studies (DIGS; [32]) were enrolled if they also had a Positive and Negative Syndrome Scale (PANSS; [33]) negative symptom score ≥20. Patients were also assessed for the presence of the deficit syndrome (DS) and for extrapyramidal symptoms (Simpson Angus Rating Scale; [34]). No cognitive testing was done in this pilot study. Demographic data collected included age, duration of illness, age of onset, and number of years of education. Patients were included only if they were in active treatment with a psychiatrist, on stable doses of antipsychotic medications for at least 4 weeks prior to entry (2 weeks for other psychotropic medications with a maximum of 3 mg/day lorazepam equivalents), and had capacity to consent. Patients were excluded if they had a true positive on a TMS Adult Safety Screen [39] were actively using drugs (urine toxicology), or had an affective or other co-morbid psychiatric disorder not in remission. This study was approved by the Columbia University/ New York State Psychiatric Institute Institutional Review Board and the FDA through an Investigational Device Exemption. All patients gave written informed consent.

rTMS

rTMS was administered with the Magstim Super Rapid (The Magstim Company Ltd, Wales, UK) and a vacuum cooled 8 inch figure eight coil at 20 Hz for 2 seconds at 100% motor threshold (MT), with an intertrain interval of 28 seconds, 40 trains for 20 days (1600 pulses per day, 32,000 total pulses), which was within safety guidelines ([35]). Motor threshold was determined weekly using electromyography (EMG). MT was defined as the lowest intensity that produced an evoked potential in the right abductor pollicis brevis with a peak-to-peak amplitude greater than 50 mV in 5 of 10 trials. Patients received rTMS treatments daily from Monday through Friday for four weeks. Consistency of coil placement across days and within treatment was monitored using the frameless stereotaxic system (Brainsight —Rogue Research) by labeling a standardized brain with the site of MT determination and the targeted site for treatment for precise repositioning of the coil. This system co-registers the patient's head in a standardized MRI space. Once the target site was determined, the coil was placed tangential to the site with the handle pointing backwards, 45° to the midsagittal line. All treatments were performed by psychiatrists trained in TMS administration who had Basic and Advanced Cardiac Life Support certification.

Assessments

The primary outcome measure was the PANSS negative symptoms subscale. We also assessed extrapyramidal symptoms (Simpson Angus Rating Scale; [34]) depression (Hamilton Depression Scale (17 item version) [36]; Calgary Depression Scale, [37]) social function (Social Adjustment Scale, [38]) and clinical impressions (Clinical Global Impressions Scale; [39]). Clinical assessments occurred at baseline, at two-week intervals during treatment, and monthly for two months at the end of treatment. Audiometry was assessed only during the active phase unless significant changes were noted.

Results

Fifteen candidate patients were screened over 6 months. Two individuals were excluded for history of seizures. One patient did not want to travel to the hospital, another declined (family contacted us), and four had primary diagnoses of bipolar disorder. Of the remaining seven (two women) who completed evaluation procedures, two were excluded (both men): the first for not meeting negative symptom criteria and the second because we were unable to obtain a motor threshold (i.e. no evoked potential elicited at 100% maximal device output). All seven were from the NY metropolitan area: 5 from NYC (4 Manhattan, 1 Brooklyn) and 2 from New Jersey. There were 2 South Asian, 1 African-American, 3 Latino, and 1 Caucasian patients. The patients lived with family (4), in residential facilities (2), and a college dormitory (1).

Five patients enrolled in the study and four completed 4 weeks of treatment. No patients had changes in medications during the study. One patient withdrew from the study in the setting of medication non-compliance with increasing delusions unrelated to the study. His psychiatrist was notified and a new treatment plan initiated. There were no adverse events (by staff administered questionnaire, e.g. seizure, headache, scalp, neck or head pain, etc.). See Table 1 for patient demographics and baseline ratings. There were no changes in depressive symptoms, extrapyramidal symptoms (low at baseline) or social deficits. Three completers showed clinically significant improvements in PANSS total scores (drops of 21%, 16%, and 13%, respectively). See Table 2 for all PANSS study ratings. There was a mean decrease in MT by 6% (3.0) from baseline to week 4, suggesting an increase in cortical excitability, although these changes were not related to negative symptom response.

The cases of the five patients who enrolled in the study are described in detail below with regard to demographics, psychiatric history (including prominent illness characteristics, negative symptoms, affective illness, substance use, and suicidality), neuroleptic medications, and treatment response.

Case 1

The first patient was a single 26-year-old male living with his father and had been unemployed since graduating from high school. He presented with a history of chronic negative symptoms, grandiose delusions and auditory hallucinations. His first psychotic episode was accompanied by significant drug and alcohol use and occurred while traveling abroad at the age of 19, following a two-month prodromal period of depressive symptoms and asocial behavior. Although the patient and his family reported that he had experienced good social functioning before the onset of his illness, he subsequently became withdrawn and lost contact with former friends. The onset of his psychosis was characterized by the acute development of grandiose delusions, restlessness, distractibility, irritability, and racing thoughts. He was eventually taken by the police to the emergency room due to aggressive and disorganized behavior.

The patient met DSM-IV criteria for schizophrenia with predominantly negative symptoms and was experiencing a single episode in partial remission that was characterized by residual negative symptoms. His illness course was continuous and chronic with deterioration in social, emotional and occupational functioning. He had experienced a great reduction in positive symptoms with medication. At the time of evaluation for this study, the patient was spending most of his time alone at home and rarely left the house. The patient reported vague and grandiose plans to accomplish something, but was unable to specify or elaborate on these intentions or how he would accomplish them. Other negative symptoms included blunted affect, stereotyped speech, and alogia. He also met criteria for the deficit syndrome with primary and stable negative symptoms of restricted affect, diminished emotional range,

poverty of speech, curbing of interests, diminished social drive and diminished sense of purpose. He also endorsed auditory hallucinations of multiple voices, religious delusions that he was God, grandiose delusions of possessing special powers, and paranoid delusions of reference.

The patient experienced a major depressive episode accompanied by suicidal ideation in the period immediately preceding his first psychiatric hospitalization, but these symptoms never recurred and were therefore brief relative to the total duration of his schizophrenia. In addition, the patient had significant marijuana and alcohol dependence in remission and a 10 pack-year smoking history. However, as the remission of his alcohol dependence coincided with the onset of psychosis and his marijuana abuse began after it, it is unlikely that his psychotic illness was directly related to the physiological effects of these substances. During his participation in this study, the patient was maintained daily on olanzapine (15mg), haloperidol (5mg) and benztropine (2mg).

He received a total of 20 rTMS treatments and had one follow-up assessment. Over the course of treatment, he spoke less about his vague grandiose plans for himself. On the PANSS, he had a 9% reduction in positive symptoms at week 4 (22% decrease on grandiosity and delusions). He had no change in his negative symptoms or social function at the end of rTMS treatment.

Case 2

The second patient was a 34-year-old Latina female living with her parents. She was single, unemployed and had no children. She presented with a history of schizophrenia, the onset of which had been characterized by her increasing isolation and academic difficulty in high school. She subsequently had four psychiatric hospitalizations for catatonia in 1999 and 2003. These episodes were characterized by stupor, rigidity, and agitation with disorganized behavior. During periods of acute psychosis, she experienced paranoid ideas of reference. These delusions were never fragmentary, widespread, nor bizarre. At baseline, she exhibited slight catatonia with awkward postures.

The patient met DSM-IV criteria for schizophrenia with predominantly negative symptoms, multiple episodes with partial recovery, social, occupational and emotional dysfunction, and medication-sensitive psychotic symptoms. Her illness course was classified as episodic with inter-episode residual symptoms that were prominently negative with severe deterioration from her functioning prior to illness onset. Although she had been able to complete high school and had plans to finish college, she was unable to articulate a plan for achieving this goal and spent most of her days internally preoccupied without hallucinations. She had difficulty tolerating social gatherings due to anxiety and a desire to be alone; at such gatherings, she greeted guests but had difficulty engaging in interpersonal interactions and quickly isolated herself. At evaluation, the patient displayed blunted affect, difficulty in abstract thinking, alogia, and poor rapport, although her insight pertaining to her illness was good. She had had several major depressive episodes over the course of her life, which were brief relative to the total duration of her schizophrenia and did not occur exclusively during periods of psychosis. She had no history of substance use or suicidality. During her participation in this study, the patient was maintained on a daily dose of risperidone (6 mg).

She completed all twenty treatments and made both follow up visits. Her positive symptoms were reduced during the course of her treatment. On the PANSS she displayed a 26% reduction in positive symptoms that was detected at week 2 and maintained at weeks 4 and 8. She had no change in negative symptoms or social function at the end of rTMS treatment.

Case 3

The third patient was a 30-year-old African female living with her family, working full-time at a fast food restaurant for two years. She had a history of two prior psychiatric hospitalizations for auditory hallucinations in 1999 and 2003. The latter hospitalization occurred 4 months after she had returned briefly to her native country, met her fiancé and gave birth to her child. During previous periods of psychosis, she experienced auditory hallucinations of music and multiple voices issuing commands, as well as delusions of reference, being controlled, mind reading, thought insertion and broadcasting, and persecution. These delusions were never fragmentary, only somewhat widespread, and not bizarre. At the time of evaluation, the patient did not have any psychotic symptoms.

The patient met DSM-IV criteria for schizophrenia with predominantly negative symptoms, including alogia, blunted affect, stereotyped and concrete thinking, poor rapport, and emotional withdrawal. Her illness course was characterized by multiple episodes with partial inter-episode recovery, social and emotional dysfunction, and medication-sensitive psychotic symptoms. She exhibited a mild deterioration from her level of premorbid functioning and failed to maintain social contacts or friendships she had had prior to illness onset. She also met criteria for the deficit syndrome with prominent symptoms of restricted affect, diminished emotional range, poverty of speech, curbing of interests (displayed little interest outside her family obligations, most of which she felt were imposed upon her), diminished sense of purpose and diminished social drive, which were severe and not secondary to medications or other symptoms. There was no history of affective illness, substance use, or suicidality. During her participation in this study, the patient was maintained on a daily dose of olanzapine (30 mg).

This patient received 20 treatments, but missed both follow up visits. At week three there were noticeable changes in the patient. The research staff commented on her increased mood reactivity, facial expression and emotional engagement in her surroundings. On the PANSS, she had a 14% reduction in negative symptoms at week 4 (50% decrease on emotional withdrawal and poor rapport, symptoms which are associated with family history of schizophrenia, [40]). She had no change in social function or positive symptoms. She also had a 16% reduction in motor threshold at week 4.

Case 4

The fourth patient was a 24-year-old unemployed Latino male living with his grandmother. He presented with a five-year history of illness and three psychiatric hospitalizations. Prior to the onset of acute psychosis at age 19, the patient experienced a three-year prodromal period in which he became more socially isolated, displayed blunted affect, held ideas of reference, and exhibited bizarre behavior such as talking to himself. Since age 19, the patient experienced continuous delusions of guilt, grandiose delusions, somatic delusions that an artificial chemical in his body was causing him to lose his memory, and delusions of mind reading of a bizarre nature. He also reported collecting bottle caps and rocks, which he would spin and play with in his hands.

The patient met DSM-IV criteria for schizophrenia with one continuous episode and a mixture of acute psychosis and concurrent negative symptoms. His illness course was relatively stable and had not changed significantly since the time of onset. At evaluation, he was socially withdrawn and his only interpersonal contacts were his grandmother and her home health attendant. He also met criteria for the deficit syndrome with primary negative symptoms of blunted affect, restricted interests, diminished sense of purpose, and diminished social drive, which were severe and not due to his positive symptoms.

The patient did not report a history of substance abuse or dependence. He experienced a major depressive episode that persisted for 4 months, but this was brief relative to the total duration of his psychosis. Although the patient's suicidal ideation precipitated his first psychiatric hospitalization, he had only made threats of suicide when depressed and never made any attempts. At evaluation, the patient was taking daily perphenazine (28 mg), clonazepam (2 mg), and paroxetine (20 mg).

After completing one week of rTMS treatment, the patient revealed he had been noncompliant with his psychotropic medications since before enrolling in the study. It was decided with his psychiatrist that since there had been no deterioration, he would remain in the study. However, after another week, he did begin to decompensate with exacerbation of his delusions. The patient was restarted on medications and thus was no longer eligible to continue due to his deterioration and the fact that participation was contingent on maintenance of stable medications.

Case 5

The fifth patient was an unmarried 24-year-old Latino college student living in a college dormitory. The onset of his illness at age 17 had been characterized by declining performance in high school and social withdrawal in the context of religious delusions as well as depressive symptoms. The patient experienced subsequent episodes of mania, accompanied by thought disorder, fragmentary grandiose and persecutory delusions and auditory hallucinations. He also experienced episodes of major depression including one that occurred after discontinuing his medications in the context of a romantic breakup.

He met DSM-IV criteria for schizoaffective disorder, bipolar type. His illness featured predominantly negative symptoms and was episodic with residual negative symptoms between acute episodes. At evaluation, he had no psychotic symptoms and did not meet criteria for a manic or major depressive episode, but displayed prominent negative symptoms of alogia, blunted affect, and social withdrawal. He found social situations difficult due to anxiety and lack of motivation. Although he reported a desire to have friends he failed to initiate calls to friends or return calls. He spent many hours alone.

The patient had a remote history of substance abuse in which he used marijuana daily for one year and suffered clinically significant impairment as a result, including depressive symptoms, suspiciousness, poor concentration, anxiety, and interference with social and academic performance. He also used methamphetamines, LSD, and combinations of these substances several times. The patient reported three suicide attempts in his lifetime in which he overdosed on zinc and iron pills and cut his wrists horizontally, the last of which occurred during a psychiatric hospitalization and required medical treatment. During his participation in this study, the patient was maintained on daily doses of aripiprazole (10 mg), lamotrigine (200mg), duloxetine (40 mg), and biweekly fluphenazine (2 mg IM).

He received all 20 rTMS treatments and made both follow-up visits. After two weeks, he began talking about social plans that he did not make. By the end of treatment, however, he was implementing some of the smaller plans (e.g. going on dates, meeting with friends in lieu of speaking on the phone) and at follow-up he had maintained attendance in a social club he started. On the PANSS, he had a 55% reduction in negative symptoms at week 4 (decreases of 50–75% on all items except the 2 absent at baseline), which were maintained at week 8.

Overall—These five patients were a diverse group including men and women, with and without the deficit syndrome. All but one had graduated high school and two had some college education. All but one had a history of depression, though only one had a history of

suicide attempt. Two patients had prior substance use, including marijuana. In the cases, treatment response was more likely in patients who displayed better overall clinical picture and social function (CGI, GAF and SAS) at baseline (though not necessarily higher educational attainment). Response of negative symptoms appeared to occur independently from depression and EPS and the negative symptoms of one patient with the DS responded to rTMS, while those of the other DS patient did not. Patients did not differ on total medications or types of antipsychotics, nor did they experience changes in depressive symptoms.

Discussion

This study examined the effect of high frequency rTMS in five patients with schizophrenia/schizoaffective disorder. Both men and women enrolled in the study, In this case series of five patients, we found that two had a reduction in positive symptoms, two had reductions in negative symptoms and one dropped out of the study. Two patients had a marked decrease in MT, suggesting increased cortical excitability, though this requires further study implementing other tests of cortical excitability. There were no adverse events and no deterioration in functioning. Patients with better baseline clinical picture and higher social function may be more likely to respond. Given the open nature and small sample size of this pilot study, however, these conclusions are made with caution. Negative symptom response in this sample was unrelated to depressive symptoms, EPS or medications, comparable to the study by Hajak et al ([22]). Patients with higher functioning may be better candidates for rTMS for negative symptoms, although this is the first study to assess baseline function as a possible predictor of response. Although we didn't expect to find changes in positive symptoms, two of the completers had reductions. Activation of fronto-temporal circuits, via transsynaptic activation by rTMS, implicated in positive symptoms [41], may be responsible for the observed reduction in symptoms.

This case series provides further preliminary evidence that high frequency rTMS to the DLPFC may reduce the negative symptoms of schizophrenia. Other open studies have had similar findings in cohorts of four [42], six [31], and ten [43] patients, respectively. This case series has several advantages over previous studies including a high number of total pulses (almost as high as Sachdev et al [42] (32,000 vs. 36,000)) and extensive clinical characterization, especially the assessment of pathology often conflated with negative symptoms, i.e. depression and EPS. To this end, we excluded patients with active affective disorders and therefore had patients with very low depression scores that were independent of negative symptom response. Hajak et al [22] also demonstrated that depressive symptoms did not account for changes in negative symptoms in their randomized clinical trial. We further assessed the presence of the DS in our sample to explore whether this patient population might respond to this novel treatment, and one of the two did.

There were technical advantages to this study as well. We used frameless stereotaxy to co-register the individual's head to a standardized brain for annotation of the DLPFC after using the 5 cm rule (anterior to the determination of motor threshold). Although we did not use the individual's own MRI, such a process allows for highly consistent re-identification of the target site each day subsequent to MT determination for each patient. All other positive studies used either the 5 cm rule without stating how they targeted the treatment site on non-MT days or the 10–20 EEG system [20–22].

This study was limited by its open-label design and by its inclusion of only five patients. We were further limited by our use of standardized MRI as opposed to individual structural MRI for DLPFC targeting to overcome inter-individual differences. Larger studies are necessary to assess whether changes in cortical excitability are associated with symptom response and

to determine if symptom response is influenced by baseline patient characteristics, such as the DS, family history, or paternal age related schizophrenia. Family history of schizophrenia, for example, has been shown to bear an association with such negative symptoms as poor rapport and emotional withdrawal, and may modulate treatment response differentially [40]. Gender effects should also be explored in future research, as studies with the highest proportions of male patients have produced negative results [23–25].

Individualized structural and/or functional targeting may enhance response and should be utilized in future research. The targeting of structures implicated in negative symptoms with respect to individual neuroanatomy is facilitated by the high spatial resolution of the combination of neuronavigational imaging devices that allow for the precise localization of magnetic coils. Such neuronavigational techniques are critical with respect to the underlying pathophysiologic symptomatology of schizophrenia, but are not yet the standard of rTMS treatment trials for schizophrenia. Furthermore, it is not clear that the DLPFC or even the left side is the optimal site for negative symptoms. Functional imaging prior to treatment may reveal more optimal treatment targets ([12]) and the results of rTMS trials targeting these sites may be informative regarding their respective roles in negative symptoms. The frequency at which rTMS is applied is particularly relevant in treating pathophysiology with respect to high versus low frequency (i.e. high frequency increases cortical excitability and low decreases it), but has yet to be optimized with regard to which high frequency would best alter cortical excitability for the treatment of negative symptoms (e.g. 10 vs. 20 Hz).

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TABLE 1

Patient Baseline Characteristics

Baseline Patient Characteristics	Enrolled (N=5) Mean (s.d.)	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Completers	4	Yes	Yes	Yes	No	Yes
Schizophrenia Diagnosis	4	Yes	Yes	Yes	Yes	
Schizoaffective Bipolar Type	1					Yes
Deficit Syndrome	4	Yes	No	Yes	Yes	No
History Depression	4	Yes	No	Yes	Yes	Yes
History suicide attempt	1	No	No	No	No	Yes
History substance abuse	2	Yes	No	No	No	Yes
Number women	2	Male	Female	Female	Male	Male
Age	27.6 (2.2)	26	34	30	24	24
Age of psychosis onset	18.8 (2.0)	19	14	25	19	17
Years of Education	13.2 (1.2)	12	17	11	12	14
Chlorpromazine equivalents	412.8 (74.6)	550	300	600	280	300
Number medications	2.8	3	2	1		5
Number medication types	2.4 (0.6)	2	2	1	3	4
Typical antipsychotic	N=3	1			1	1
Atypical antipsychotic	N=3	1	1	1		1
Anticholinergic	N=2	1	1			
Antidepressant	N=2				1	1
Mood stabilizer	N=1					1
Benzodiazepine	N=1				1	
Other	N=1					1
Simpson Angus Rating Scale	1.4 (0.6)	1	3	2		1
PANSS						
Positive	16.2 (2.6)	23	19	11	17	11
Negative	28.8 (2.6)	32	28	33	31	20
General	36.6 (3.9)	46	42	26	36	33

Baseline Patient Characteristics	Enrolled (N=5) Mean (s.d.)	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Total	81.6 (7.4)	101	89	70	84	64
HAM-D (17 item)	9.4 (2.8)	7	12	4	18	6
SAS	59.8 (10.8)	68	67	49	69	47
CGI	5.0 (0.7)	6	6	4	6	3
GAF	47.0 (4.2)	40	40	50	45	60
Motor Threshold	56.6 (7.7)	52	37	76	68	50

PANSS, Positive and Negative Syndrome Scale; HAM-D, Hamilton Depression Scale; CGI, Clinical Global Impressions; GAF, Global Assessment Factor; SAS, Social Adjustment Scale.

Table 2

Patient PANSS' scores across the study

	Baseline	Week 2	Week 4	Week 8	Week 12
Case #1					
Positive	23	17	18	20	N/A
Negative	32	31	32	37	N/A
General	46	32	45	37	N/A
Case #2					
Positive	19	14	15	14	20
Negative	28	32	32	33	29
General	42	47	50	46	45
Case #3					
Positive	11	11	14	N/A	N/A
Negative	33	28	25	N/A	N/A
General	26	20	24	N/A	N/A
Case #4					
Positive	17	21	N/A	N/A	N/A
Negative	31	36	N/A	N/A	N/A
General	36	49	N/A	N/A	N/A
Case #5					
Positive	11	11	10	10	9
Negative	22	18	9	12	17
General	34	27	19	22	24