CHAPTER NINE

Treating Thought Disorders

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THOUGHT DISORDERS, PSYCHOSIS

A thought disorder is defined as any disturbance of thinking that affects language, communication, or thought content. Manifestations range from simple blocking and mild circumstantiality to profound loosening of associations, incoherence and delusions, characterized by a failure to follow semantic and syntactic rules that is inconsistent with the person's education, intelligence or cultural background.[1] It may involve difficulty putting cohesive thoughts together, or making sense of speech or a disturbance in one's ability to generate a logical sequence of ideas, as indicated by disordered speech and/or writing.

There are different types of thought disorders. A flight of ideas refers to language that may be difficult to understand because it switches quickly from one unrelated idea to other. Circumstantiality refers to language that may be difficult to understand, because it is long-winded and convoluted in reaching its goal. Word salad refers to words that are inappropriately strung together, resulting in gibberish.[1]

Since the early work of Bleuler,[2] Kraepelin,[3,4] and Moukas et al.,[5] thought disorder has been considered a major symptom of psychosis. Symptoms of psychosis are similar, independent of the clinical diagnosis. Patients with different diagnoses can have the same behaviors and treatment responses as with psychosis. Although psychosis is not unique to disorders such as schizophrenia, they may share a common neurophysiological substrate even though there may be various specific causes of the psychosis in different diagnostic groups. For example, thought disorders often are seen in those who have been given a diagnosis of schizophrenia or a schizophrenia-like disorder, bipolar disorder (manic episode, i.e., with psychotic symptoms), depression with psychotic features, traumatic brain injury (TBI)-induced axis I disorders (depression, bipolar disorders,

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schizophrenia and psychosis) and epilepsy,[6] and also are present to various degrees in anxiety disorders.[7–9]

Large population studies show that people with a history of epilepsy have nearly 2.5 times the risk of developing schizophrenia, and nearly three times the risk of developing a schizophrenia-like psychosis as the general population,[6] and the rate for the development of schizophrenia following a TBI is 1%.[8] Furthermore, even an initial TBI may place an individual at risk for sustaining a delayed-onset psychosis, such as schizophrenia, and for subsequent brain injuries independent of the psychosis.[10] The development of psychosis may be a delayed sequela of the pathophysiological changes resulting from either an earlier or a later TBI.[11] Persons with risk factors for developing a psychosis secondary to TBI are more likely to have had a previous congenital neurological disorder or to have sustained a head injury prior to adolescence.[12]

Lifetime incidence rates of TBI survivors who later demonstrate psychotic symptoms vary across studies, varying from 3.4% to 8.9%.[13,14] The onset of psychosis after TBI is highly variable but is generally delayed. In their study of World War II veterans, Achte et al.[15] reported that the occurrence of psychotic symptoms ranged from 2 days to 48 years after injury, with 42% experiencing their first psychotic episode 10 or more years after sustaining a missile wound to the head. Fujii and Ahmed[16] reported a range from 3 months to 19 years, with a mean onset of 5.9 years after closed head trauma. Feinstein and Ron[17] reported a mean latency of 11.7 years, with a range of 0 to 52 years.

There are several similarities between psychotic phenomena and unwanted intrusive thoughts (UITs). Garety and Hemsley[18] found that many patients with delusional beliefs scored highly (8 or more out of 10) on characteristics that are commonly associated with UITs (e.g., resistance [69%] and interference [47%]). It has also been noted that hallucinatory phenomena share many characteristics with UITs.[19] Auditory hallucinations (AHs) commonly have external precipitants,[20] as do UITs,[21] and these often increase with stress,[20] as do UITs.[22]

The co-occurrence of anxiety disorders may mediate some of the social and functional impairment well known in schizophrenia. Huppert and Smith's[23] finding that hallucinations were also related to self-reported obsessive-compulsive disorder (OCD) symptoms leads to a broader possibility: neurophysiologically, there may be an overlap between OCD symptoms and positive symptoms such as seen in schizophrenia, because the neural circuits known to relate to both types include the orbitofrontal cortex and the anterior cingulate cortex (ACC).[24,25]

Several studies show an association between thought disorders and cognitive impairment,[26–28] which suggests a common neurobiological substrate for both dysfunctions. Additionally, a meta-analysis by Kerns and Berenbaum[29] revealed a correlation between formal thought disorders (FTDs) and executive functions, and connections between thought disorders and semantic memory. Recently, thought disorders have been linked with both structural and dynamic abnormalities of the language system in the brain, which may indicate a common neurobiological basis underlying, for example, thought disorders and AHs.[30,31] Research suggesting that thought-disordered patients lack some constituent cognitive function is consonant with the notion that contextual deficits in thought-disordered patients with schizophrenia are a central issue. Defects in cognitive processing efficiency in schizophrenia seem to involve deficits in tasks that place heavy emphasis on selective attention.[32] The functions of a central executive system, elaborated on by Baddeley,[33,34] have been implicated in schizophrenia. They begin to describe coordinative functions that might be employed in selective attention, such as dividing attention, focusing on a subset, or switching attention – all of which appear demonstrably affected in patients with schizophrenia. Studies in priming also demonstrate how attention may be impaired because of disinhibited activation of semantic networks, thus impairing the ability to focus or attend to a specific subset of information. Thought-disordered subjects with high levels of impairment show inhibited semantic priming effects greater than those of less impaired thought-disorder subjects, suggesting aberrations in the activation of cognitive semantic networks.[35]

Andreasen and Grove[36] found that FTD has predictive value with regard to prognosis over several months in persons with psychiatric diagnoses. They found that negative thought disorder seems to predict the short-term outcome of schizophrenia. Patients with poverty of speech and poverty of content were more likely to have a form of schizophrenia, whereas positive forms of thought disorder were more common among the affective psychoses.[3,4,36–38]

qEEG, NEUROIMAGING STUDIES, VARETA, LORETA

Many data show that brain electrical activity reflects subtle aspects of brain function, including information processing and cognition. Many individuals suffer from disorders of these functions. An unknown but perhaps large percentage of them might benefit from intervention if precise diagnostic information were available. Although current psychological and

neurological methods are not sufficiently sensitive for this purpose, electrophysiological measurements of brain functions related to information processing might be of substantial value.[39]

When looking electrophysiologically at patients with different diagnoses who share psychotic features, it has been found that those with very different clinical diagnostic labels share features that appear to be distinctive for psychosis, and it also has been demonstrated that such features do not depend upon the duration of illness or medication effects.[40] Based on a study conducted by John et al.[40] on psychotic patients that included schizophrenics, depressives and alcoholics, the authors postulated that it would be desirable to subtype psychotic patients based on their quantitative electroencephalogram; and because different subtypes may need different interventions, it would be possible to individualize treatments for the psychotic patient. One of the interventions that they specifically mentioned was neurofeedback, which would be able to target and correct the specific electrophysiological deviations (from norm) of the subtype, which, in turn, would serve to correct the specific neurotransmitter imbalances. Relevant to this, schizophrenic subtypes and their response to risperidone or to haloperidol have been identified by Czobor and Volavka.[41,42]

Abnormal EEG findings are seen in 20–60% of schizophrenic patients.[43–45] Most often, EEGs have been characterized by decreased alpha activity and/or increased beta activity.[46–49] Others have reported shifted alpha mean frequency or reduced alpha responsiveness[44,46,50] and increased slow activity.[51,52] Negative symptoms have been correlated with delta waves, especially in temporal areas,[53] coupled with decreased alpha and increased beta. Studies have shown greater coherence in patients than in healthy controls.[54,55] Increased interhemispheric coherence over frontal regions may distinguish schizophrenia patients from those suffering from bipolar depression, who are more likely to show decreased frontal coherence.[56,57] Ropohl et al.[58] found abnormally large beta oscillations localized around the left auditory cortex in a schizophrenia patient with treatment-resistant AHs. Left hemisphere source phase-locking factor (PLF) in schizophrenia was positively correlated with AH symptoms, and was modulated by delta phase. The correlation between source-evoked power and PLF found in healthy controls was reduced in schizophrenia for the left hemisphere sources.[59]

qEEG studies have shown discriminant accuracy as high as 95.67% in the detection of mild head injury,[60] and >75.8% accuracy in the prediction of outcome one year after injury.[61] These findings have been confirmed

by recent studies.[62–65] Persons with major depression can be differentiated from normal controls with a specificity of 91.3% and sensitivity of 91.3%.[66] Such accuracy helps in the differential diagnosis, as between thought disorder resulting from a TBI and that caused by schizophrenia, thereby providing valuable information for the selection of treatment. Currently, the evidence for differential medical treatment is equivocal.

In region of interest analyses, structural abnormalities in the left superior temporal gyrus (STG),[67,68] the left planum temporale[69,70] and the orbitofrontal cortex[71] have been linked to a FTD in schizophrenia patients. Most findings of structural abnormalities associated with FTD were reported in the STG. Recent results point toward structural abnormalities linked to FTD beyond the STG.[31] The severity of FTD was negatively correlated with the gray matter volume of the left superior temporal sulcus, the left temporal pole, the right middle orbital gyrus and the right cuneus/lingual gyrus. Structural abnormalities specific for FTD were found to be unrelated to gray matter differences associated with schizophrenia in general. The specific gray matter abnormalities within the left temporal lobe may help to explain language disturbances included in FTD.[72] Severity of FTD was correlated with a disruption of the left semantic network in schizophrenic patients. Horn et al.'s[72] work suggests that FTD is a consequence of a frontoparietal/temporal disconnection caused by a complex interaction between structural and functional abnormalities within the left semantic network.[73]

Although the signs and symptoms of schizophrenia may be multifaceted, neurobiological and behavioral data are beginning to show that a common element in schizophrenia is the dysregulation of emotional arousal (e.g., the hyperarousal associated with paranoid symptoms[74] and the hypoarousal associated with negative symptoms[75]), and cognitive deficits secondary to both hyper- and hypoarousal.[76]

The persistence of some level of thought disorder, even during periods of remission and drug treatment, is especially notable in schizophrenic patients. Severity of thought disorder is, in part, state- and medication-related.[77,78] Severe thought disorder, especially in schizophrenic patients, is strongly predictive of worse functional and social outcomes.[78,79] Paranoid schizophrenia tends to be related to differences in Brodmann areas (BA) 10 and 46 and the prefrontal–limbic circuit.[80,81] 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 prefrontal–limbic negative feedback loop.[82,83] This may be

related to the excitatory component of the amygdala[84,85] and the inhibitory component provided primarily by the prefrontal regions.[86,87]

Evidence from functional magnetic resonance imaging (fMRI) studies also showed that schizophrenic patients show significantly lower connectivity between left temporal cortex and left dorsolateral prefrontal cortex.[88,89] McCarthy-Jones[90] concluded that the most consistently documented areas involved in auditory verbal hallucinations are the STG, the left inferior frontal gyrus, and the arcuate fasciculus tract connecting them. It was suggested that because this neuronal geography is clear, it makes targeted neurofeedback feasible.

In a related study investigating the electrophysiology of auditory verbal hallucinations, Koutsoukos et al.[91] found theta–gamma frequency interaction differences, especially in the left temporal area, to be statistically significant for subjects experiencing such symptoms.

Based on a cluster analysis of electrophysiological measures conducted by John et al.[40] on 390 psychotic patients that included schizophrenics, depressives and alcoholics, six different clusters were identified. Using variable resolution electromagnetic tomographic analysis (VARETA – a source localization analysis of electrophysiological signals), all six clusters were found to have increased power in the excited systems, which comprised a set of subcortical regions that included limbic structures (amygdala, hippocampus, posterior cingulate), the basal ganglia and the thalamus. Cortical sources common to all clusters included the precentral gyrus, the middle and the STG. Also, they had depressed activity in the hippocampus and the occipital lobe. Low-resolution electromagnetic tomographic analysis (LORETA source analysis) studies in unmedicated patients with schizophrenia have mainly implicated slow frequencies,[92–94] probably reflecting cortical hypoactivation, and indicated a condition of abnormal functional connectivity within frontal and temporoparietal networks.[93–95] LORETA source-localization findings also support and extend the notion that the parietal lobe plays a crucial role in the pathogenesis of psychosis,[96] and that default mode network (DMN) dysfunction may be a core neurobiological feature in both schizophrenia[97] and schizophrenia-like psychosis, as sometimes seen in epilepsy.[96] In one study neuroleptic-naive patients with schizophrenia were compared to age- and sex-matched healthy controls, and data were analyzed by LORETA. Values for delta band activity were greater for patients in the left inferior temporal gyrus, right middle frontal gyrus, right superior frontal gyrus, right inferior frontal gyrus and right parahippocampal gyrus, and were negatively correlated with negative – but not

positive – symptoms.[98] Phase locking in the gamma-band range has been shown to be diminished in patients with schizophrenia, and there have been reports of positive correlations between phase locking in the gamma-band range and positive symptoms, especially hallucinations. A major LORETA finding was reduced phase synchronization in schizophrenia between the left and right primary auditory cortex (Heschl's gyrus), but not between the bilateral secondary auditory cortices.[99,100] Comparisons of spectral analyses of the qEEG and LORETA of schizophrenia patients with treatment-refractory AHs, lasting for at least 2 years, with those of schizophrenia patients with nonauditory hallucinations (N-AH) in the past 2 years, showed significantly increased beta 1 and beta 2 frequency amplitude in AH compared with N-AH patients. Gamma and beta (2 and 3) frequencies were significantly correlated in AH, but not in N-AH patients. LORETA revealed significantly increased beta (1 and 2) activity in the left inferior parietal lobule and the left medial frontal gyrus in AH than in N-AH patients.[101]

The similarity between attention deficit hyperactivity disorder (ADHD) and schizophrenia was investigated in a study where matched ADHD subjects, schizophrenic patients and normal controls (100 subjects in each group) were compared using a cued GO/NOGO task. The action suppression component (generated in the supplementary motor cortex) was shown to be reduced in the ADHD group and was almost completely absent in the schizophrenia group. The conflict monitoring component was moderately reduced in ADHD and schizophrenia groups, whereas the sensory-related independent components remained practically the same in all three groups.[102]

The anatomical basis for the OCD-type thought disorder is complex and still under investigation, although ACC abnormalities are consistently being seen in the pathophysiology of OCD.[103] Anatomically, the ACC can be divided into cognitive (dorsal) and emotional (ventral) components. The dorsal part of the ACC is connected with the prefrontal and parietal cortices, as well as with the motor systems and frontal eye fields.[104] The ventral part has connections to the amygdala, the nucleus accumbens, the hypothalamus and the anterior insula. It is involved in assessing the importance and relevance of emotional and motivational information. A number of SPECT studies report hyperfrontality (increased right and left anterior prefrontal cortex activity and increased anterior cingulate gyrus activity) and increased basal ganglia activity in OCD.[105]

In a study using LORETA analysis, OCD patients who responded to antidepressants exhibited significantly lower activity in beta bands in the rostral anterior cingulate (BAs 24 and 32) and the medial frontal gyrus

(BA 10), suggesting that a distinctive pattern of activity within the medial surface of the frontal lobe predicts therapeutic response in OCD.[106] In the premedication recordings an excess current source density in the beta frequencies in the cingulate gyrus was revealed by LORETA. The beta frequencies (beta 2 [16–20 Hz], beta 3 [20–24 Hz] and beta 4 [24–28 Hz]) involved were located primarily in the middle cingulate gyrus as well as adjacent frontal and parieto-occipital regions. Other studies have found that individuals with OCD symptoms have excess beta activity in the cingulate gyrus compared to a non-OCD control group.[107] This is consistent with qEEG study findings of excess central beta.[108] The findings suggest that in addition to these regions, overactivation of the middle cingulate gyrus also plays an important role in OCD symptoms.[107] In Velikova et al.'s[109] study, the brain electrical activity of OCD patients showed increased current density for delta in the insula, and for beta in the frontal, parietal and limbic lobes. OCD subjects also had decreased interhemispheric coherence and reduced coupling between delta and beta frequencies. They concluded that in OCD increased frontal beta is consistent with previous evidence of frontal dysfunction.

PSYCHOPHARMACOLOGICAL TREATMENT

Psychopharmacological treatment can suppress psychotic symptoms in most patients with schizophrenia, but about 20% remain resistant to the antipsychotic effects of neuroleptic therapy and continue to manifest delusions and hallucinations as well as FTD.[110] The challenge of treatment-resistant schizophrenia continues despite the advent of a second-generation class of antipsychotics. The widespread off-label use of combination therapies of two, three or even four antipsychotic drugs is an indication that many clinicians still encounter a substantial number of patients who do not adequately respond to the approved doses of antipsychotic medications.[110] The comorbidity of OCD in schizophrenia may contribute to treatment resistance. Among 118 outpatients with schizophrenia, 8.8% had clinically significant OCD symptoms as measured by the Yale–Brown Obsessive Compulsive Scale (Y-BOCS).[111] The higher the Y-BOCS score, the greater the positive symptoms measured by the positive and negative syndrome scale (PANSS), especially delusions. Some studies have found a higher prevalence of OCD symptoms up to 25% in schizophrenia.[112] Treatment of this comorbidity may be complicated by the fact that, according to a series of case reports, the use

of atypical antipsychotics in monotherapy may be associated with the de novo appearance of, or the aggravation of, preexisting OCD symptoms in a small proportion of patients with schizophrenia.[113] On the other hand, the addition of atypicals to selective serotonin reuptake inhibitors (SSRIs) has been shown to increase the response of OCD patients who have failed to respond adequately to SSRIs.

With OCD, a moderate amount of evidence suggests that atypical antipsychotic medications have clinically important effects when used as augmentation therapy for 8–16 weeks in patients with OCD resistant to standard treatment. Only risperidone, olanzapine and quetiapine have been studied. The evidence for benefit with risperidone and quetiapine is stronger than for olanzapine.[114]

Typical antipsychotic medications are commonly used to control TBI-induced agitation and psychosis. However, there are no controlled antipsychotic medication studies, or evidence other than case studies, concerning psychosis after TBI. Case studies (varying between one and nine patients) of atypical antipsychotic agents such as clozapine, risperidone and olanzapine given to TBI patients showed mixed results.[115–117]

It is evident that more effective treatment modalities are needed in treatment-resistant schizophrenia, or any form of thought disorder, to address the needs of patients who remain substantially symptomatic and disabled even with the use of currently available antipsychotic agents.

SCIENTIFIC EVIDENCE OF NONMEDICATION TREATMENT MODELS IN PSYCHOSIS

Electroconvulsive Therapy

The use of electroconvulsive therapy (ECT) to treat schizophrenia was introduced in 1938. A review of studies of combined ECT and antipsychotics for schizophrenia did not necessarily address whether this approach is effective in cases of treatment resistance.[118] A review of the literature on the efficacy of ECT[119] involving placebo-controlled studies showed minimal support for effectiveness with either depression or schizophrenia during the course of treatment (i.e., only for some patients, on some measures, and sometimes perceived only by psychiatrists but not by other raters), and no evidence, for either diagnostic group, of any benefits beyond the treatment period. There are no placebo-controlled studies evaluating the hypothesis that ECT prevents suicide, and no robust evidence from other kinds of studies to support that hypothesis.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Investigation of the influence of rTMS on functional brain responses in healthy subjects has revealed an increased connectivity between the right temporoparietal cortex and the dorsolateral prefrontal cortex and the angular gyrus in subjects who had received rTMS. These findings have been interpreted as indicators of normalization of functional connectivity between these regions, which might support therapeutic effects of rTMS, e.g., for schizophrenic patients.[120] Neuroimaging studies have implicated left temporoparietal hyperactivity during AHs,[121] and related therapeutic studies have shown reduced severity of hallucinations with low-frequency rTMS (putatively reducing cortical excitability) with the stimulation coil applied midway between T3 and P3 (using the 10–20 EEG international system).

Two randomized, double-blind, sham-controlled trials of treatment-refractory AHs in patients with well-defined treatment-resistant schizophrenia produced conflicting results. In one study no significant improvement occurred in total mean PANSS score, either in its positive or its AH subscales, among active-treatment patients compared to controls.[122] In the other study[123] a significant improvement in the mean PANSS positive subscale score occurred in active-treatment patients, regardless of which hemisphere was stimulated, compared to controls. However, a meta-analysis study indicated that rTMS at 1 Hz applied to the temporoparietal region once on several consecutive days may reduce AHs.[124]

In another study, low-frequency rTMS (0.9 Hz, 100% of motor threshold, 20 min) applied to the left temporoparietal cortex was used for 10 days in the treatment of medication-resistant AHs in schizophrenia. They found a significant improvement in total and positive symptoms (PANSS), and on the hallucination scales, and a decrease in current densities (LORETA) for the beta 1 and beta 3 bands in the left temporal lobe, whereas an increase was found for the beta 2 band contralaterally.[125]

Slow rTMS, at a frequency of 1 Hz, has been proposed as a treatment for AHs. Some meta-analyses have supported this approach, reporting a substantial effect size (d values 0.515–0.88) of low-frequency rTMS on hallucinations.[126–129] However, results have been inconsistent, with two recent studies reporting no effect.[129,130]

The systems involved in speech generation and perception are broad and involve frontal as well as temporoparietal areas.[131] Only a few studies have examined low-frequency rTMS targeting these broader brain regions. Although increased activation has been reported in Broca's

area,[132] its right homologue,[133] Heschl's gyrus,[99,134,135]and the middle and STGs,[131,136,137] stimulation of these areas with rTMS was not found to be more effective than sham stimulation.[138–142] High-frequency rTMS stimulation (putatively increasing neuronal excitability) over the prefrontal cortex has shown some promise in improving negative symptoms in schizophrenia.[143] Based on three meta-analyses conducted on the effects of rTMS on negative symptoms,[127–144] a mild to moderate effect size was observed. The effect size increased when only AHs were targeted, and when the stimulation time was increased.[145]

The evidence generally suggests that rTMS can modulate cortical excitability to improve refractory auditory verbal hallucinations in schizophrenia.

Transcranial Direct Current Stimulation (tDCS)

Hasan et al.'s[146] study concerned schizophrenia patients who were clinically stable and who were divided into two groups. One group consisted of patients who had had a single psychotic episode (lasting at least 1 month), no relapse, and duration of psychosis <2 years (recent-onset schizophrenia). The second group included patients with more than two psychotic episodes, at least one relapse, and a duration of psychosis >2 years (multiepisode schizophrenia). These latter patients displayed a more chronic course of schizophrenia. The patient groups were matched with healthy subjects. Schizophrenia patients with multiple psychotic episodes displayed significant deficient long-term potentiation, such as plasticity, as reflected in a reduced motor-evoked potential increase after anodal tDCS, compared to healthy subjects and patients with recent-onset schizophrenia.

In healthy adults, probabilistic association learning, which involves a gradual learning of cue–outcome associations, activates a frontostriatal network. Studies of probabilistic association learning in schizophrenia have shown frontostriatal dysfunction, although considerable heterogeneity in performance has also been reported. Anodal tDCS to the dorsolateral prefrontal cortex has been shown to improve probabilistic association learning in healthy adults[147] and might be predicted to do so in schizophrenic patients. Although anodal tDCS failed to improve probabilistic association learning based on the performance of the whole healthy sample, greater variance in the active relative to the sham conditions suggested that a subset of people may respond to treatment.

In a first single-case pilot study Homan and colleagues[148] found improvements in clinical symptoms accompanied by a decrease in regional

cerebral blood flow in the frontal and temporal lobes, indicating that tDCS can have a specific neurobiological effect.

It has been suggested that the application of tDCS with inhibitory stimulation over the left temporoparietal cortex and excitatory stimulation over the left dorsolateral prefrontal cortex could affect hallucinations and negative symptoms, respectively. In the study by Brunelin et al.,[149] 30 patients with schizophrenia and medication-refractory auditory verbal hallucinations were randomly allocated to receive either 20 minutes of active 2-mA tDCS or sham stimulation twice a day on five consecutive days. The authors assessed the efficacy of tDCS administered to the left temporoparietal junction ("inhibitory" cathodal tDCS) and the left dorsolateral prefrontal cortex ("excitatory" anodal tDCS) in reducing the severity of refractory auditory verbal hallucinations in patients with schizophrenia. They also assessed the impact of this technique on other refractory schizophrenia symptoms. Auditory verbal hallucinations were robustly reduced by tDCS after 10 active sessions over five days' tDCS compared to sham stimulation. There was a mean diminution of 31%, compared with an 8% reduction after 10 sham sessions. At the end of the trial, six patients (40%) could still be categorized as responders (defined as a >50% reduction in Auditory Hallucinations Rating Scale score), and this has not been the case in rTMS studies.[127–129] The beneficial effect on hallucinations lasted for up to 3 months. The authors also observed an amelioration of other symptoms with tDCS, as measured by the positive and negative syndrome scale ($d = 0.98$, 95% CI 0.22–1.73), especially for the negative and positive dimensions. No effect was observed on the dimensions of disorganization or grandiosity. The results show promise for tDCS in treating refractory auditory verbal hallucinations and other selected manifestations of schizophrenia.

Cranial Electrotherapy Stimulation (CES)

In one study it was found that anxiety and depression scores improved significantly in a CES treatment group but not in a placebo (sham treated) group, or in a "wait in line" control group of persons with mild TBI.[150] In another study evidence was found that CES reduces aggression in violent neuropsychiatric patients (16 schizophrenia, 10 schizoaffective disorders, one psychosis, two bipolar disorder).[151]

With regard to mechanisms through which this treatment modality may work, Feusner et al.'s[152] study provides evidence that CES stimulation may result in cortical deactivation, as well as altering brain connectivity in the DMN. In patients with anxiety and those with depression, one

possibility is that alterations in the DMN may have a therapeutic effect of disengaging worry or rumination-promoting internal dialogue,[153] and/or promoting attention to external stimuli.

Deep Brain Stimulation

Deep brain stimulation (DBS) is a surgical treatment in which a device called a neurostimulator delivers tiny electrical signals to the areas of the brain that control movement. DBS has emerged as a treatment for severe cases of therapy-refractory OCD, and promising results have been reported. However, the published results are limited and the method is currently experimental.[154] Although no DBS studies have been conducted in schizophrenia, in cases where OCD is comorbid with schizophrenia, DBS may prove to be an effective treatment modality.

Computer-Based Cognitive Training

Cognitive training is an important aim of treatment for patients with schizophrenia. In a multicenter study, 64 patients with schizophrenia were investigated before and after completing a 5-week course of computer-based cognitive training using the program "Cogpack." Besides improvements in cognitive function (primary effect), patients enjoyed the training and reported increased self-esteem and progress in using computers (secondary effects). Computer-based anxiety scores at the onset of treatment did not exceed normal values. After completion of the training, these scores were significantly reduced and subjective reports of wellbeing significantly increased.[155]

Treating Thought Disorders with Neurofeedback and Biofeedback

Dr Andrew Abarbanel, in discussing how neurofeedback is useful in ADHD, stated that neural networks controlling the attention processes could be adjusted by neuromodulation, and in the long term could be transformed into a stable state, with longer-lasting results than with pharmacological treatment. He further postulated that this form of neuromodulation (neurofeedback) would be useful in depression, OCD and schizophrenia, because different behavior processes are controlled by similar neuropsychological mechanisms that can be self-modulated.[156]

In all forms of biofeedback operant and, in some cases classical, conditioning is considered to be the basic mechanism through which effects are mediated.

In 2000 Eric Kandel[157] won a Nobel Prize for showing that the synaptic mechanisms of classical conditioning and operant conditioning (including RNA/DNA mechanisms) are universal throughout the animal kingdom, including humans. There are also sensitization and habituation, which are scientifically understood but not generally effective, or do not have long-lasting effects and do not involve the same plasticity mechanism as operant and classical conditioning. Evidence of this plasticity was demonstrated in an fMRI study conducted by Ghaziri et al.,[158] who conducted fMRI feedback training in healthy subjects using an attention paradigm with a sham control. In the active treatment, group scores on the Integrated Visual & Auditory (IVA) full scale attention quotient (which is based on measures of both visual and auditory attention) significantly increased in comparison to baseline, and IVA subtest scores on auditory attention were also significantly higher following neurofeedback. For participants in the sham group, scores on visual attention were greater after training, but no difference in overall attention performance was noted. More importantly, a significantly greater than baseline increase in gray matter volume was found for the active neurofeedback group in a number of cortical areas. These were located in the right hemisphere (RH; inferior, middle and superior frontal gyri; inferior parietal lobule; inferior temporal gyrus), and in the left hemisphere (LH; inferior and superior frontal gyri; inferior and STGs; superior parietal lobule). With regard to white matter, significant increases in fractional anisotropy were measured in the superior longitudinal fasciculus (LH), inferior longitudinal fasiculus (LH) anterior limb of the internal capsule (LH), anterior corona radiata (RH), cingulum (RH) and (LH), and corpus callosum (genu, body, splenum). No change in gray and white matter was noted for members of the sham and control groups. These findings suggest that neurofeedback therapy can induce changes in brain regions implicated in attention. Their findings also indicate that neurofeedback therapy can produce modifications in white matter tracts involved in attentional processes. Ros et al.[159] were able to show that at around 30 minutes after training, neurofeedback induced a statistically significant upregulation of functional connectivity within the dorsal anterior cingulate/mid-cingulate cortex of the salience network in the experimental group, but not in the sham group. Therefore, by using fMRI neurofeedback and a placebo-control group, they were able to extend the findings of Ros et al.[160] demonstrating that the adult cortex is sufficiently plastic that a mere half-hour of targeted volitional activity (i.e., neurofeedback) is capable of intrinsically reconfiguring the brain's functional activity

to last above and beyond – or at least as long as – the period of training itself.

There has been some reported research using fMRI neurofeedback and other forms of neurofeedback with clinical populations. For example, in a pilot study with real-time functional magnetic resonance imagining conducted by Ruiz et al.,[161] schizophrenic patients were able to train the self-activation of the right insula, resulting in improved performance on a face recognition task.

There is empirical evidence that neurofeedback can help with brain regulation in ADHD, impaired social skills of children with ADHD,[162–164] seizure disorder,[165] substance abuse,[166–169] depression,[170–173] personality and mood instability,[174,175] and can significantly improve or redress many of the symptoms of patients with postconcussion syndrome (PCS),[176–179] as well as improving similar symptoms in non-PCS patients.[179]

Various theories have been proposed as to why neurofeedback can be helpful in so many disorders. One reason is that several disorders may stem from dysregulation in the same neural regions or networks. For example, DMN dysfunction is seen in the pathophysiology of schizophrenia, epilepsy, anxiety/depression and ADHD.[180]

The FPO2 site has been found to be relevant in the treatment of both fear and anxiety problems. It is a site that has been found to access the amygdala, which is a structure often disturbed or dysregulated in both schizophrenia and anxiety. FPO stands for frontal pole orbital (prefrontal) and "2" signifies the right side of the brain. 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.[176–179,181]

Another theory is that by engaging principally with the DMN, the salience network, and the central executive network, thought disorders can be treated. This is based on a model that postulates that much of psychopathology is traceable to dysregulation of the interaction among these three resting state networks. There is some speculation that infra-low-frequency neurofeedback training may provide the most direct access to the dynamics of these interactions.[182]

Recently there have been some applications of an EEG inverse solution to neurofeedback. Using LORETA modeling, it is possible train a functional area of the brain, for example the anterior cingulate (cognitive division) to improve sustained attention. Possible applications of the technique include the discovery and treatment of epileptic foci, the rehabilitation of specific brain regions damaged as a consequence of TBI, and, in

general, the training of any spatially specific cortical electrical activity.[183] LORETA neurofeedback in the ACC appears to induce long-term cortical changes and produces significant positive increases in working memory and processing speed scores.[184]

As stated previously, because OCD symptoms and positive symptoms overlap, and because the neural circuits related to these symptoms are common, the training of these circuits may be especially important in the treatment of both OCD and thought disorders. An uncontrolled study by Sürmeli and Ertem[185] gave a detailed description of the neurofeedback protocols used that have been found to be helpful in OCD.

We have found that with neurofeedback, a general rule is to link the patient's symptoms to deviant Z-scores noted at scalp electrode sites above cortical regions with known functional specializations related to the patient's symptoms.[186,187] The importance of proper location and frequency band selection was also shown by Moore in a review of two OCD studies he conducted, where he found that pure alpha training did not produce any results. He concluded that this was because there were two OCD subgroups, neither of which would have been expected to benefit from alpha training.[188]

In an OCD study conducted by Sürmeli and Ertem[185] the case study group assessed showed improvement in scores on the Y-BOCS. The magnitude of the improvement was 21.53 points, which was almost double the 10.64-point average improvement seen with drug treatment by Ackerman and Greenland.[189] Furthermore, after 2 years of follow-up, of the 36 original patients 19 remained symptom free or improved; nine had developed mild symptoms that did not interfere with their daily functioning and who did not feel the need to seek treatment; and five had relapsed. Of the two patients who received medication during treatment, one was in the group that did not respond to treatment. That patient also did not respond to medication and was in the follow-up relapse group. The other patient who received medication responded well to neurofeedback treatment and remained improved and medication free.

In a study on PCS, 20 out of 40 drug-free patients had some sort of psychotic symptom (20 with paranoia, one with visual hallucinations and four with AHs). All of these patients' symptoms resolved after neurofeedback treatment without antipsychotics being given.[176]

If Leff and Vaughn's[190] finding that the likelihood of relapse in schizophrenic persons is significantly greater in those living in high-stress homes than in those living in low-stress homes is accurate, we may conclude that

psychosocial stress can induce psychosis,[191] and that a schizophrenic person's ability to cope with stress is one of the important factors in preventing relapse.[192]

Initial studies show that some schizophrenic patients can learn to cope with stress by using relaxation therapy combined with forms of biofeedback. In one study, a biofeedback group reduced its postsession electromyographic (EMG) levels by 40%. There are several controlled[193,194] and uncontrolled[195–198] studies of successful stress reduction with biofeedback in schizophrenia. Hawkins et al.,[199] using relaxation therapy and thermal biofeedback in a controlled study of 40 long-term inpatients with schizophrenia, found no significant differences in anxiety reduction between the experimental group and the control group. One-year follow-up and post hoc analyses, however, indicated a subgroup of "anxious" schizophrenics who showed a substantial reduction in anxiety following treatment with biofeedback and relaxation.

In the 1960s Von Hilsheimer and Quirk[200] reportedly restored schizophrenics to normal life at the Clark Psychiatric Institute at Queen Street Hospital, in Toronto, Canada. Of 150 patients, 143 were discharged after self-regulation galvanic skin resistance training. This group had an average hospitalization time of 9 years (maximum 45 years). After the biofeedback treatment, they remained out of hospital for a follow-up period of three years.[200]

Although these were biofeedback paradigms and not neurofeedback, they demonstrate the feasibility of operant conditioning with schizophrenia; and the path is clear to examine the efficacy of neurofeedback therapeutic interventions in schizophrenia and the schizotypal spectrum.[201]

Nine schizophrenic patients participated in a study by Schneider and Pope[202] that explored whether EEG feedback techniques could effect changes in the EEG similar to those associated with neuroleptic-induced improvement. During five sessions, each patient was presented with feedback signals that continuously reflected the discrepancy between characteristics of the patient's EEG power spectral profile and spectral profile characteristics associated by past research with neuroleptic-induced clinical improvement. Significant within-session changes were observed for two of three EEG power spectrum bands of interest. However, no significant session-to-session EEG changes were observed. The results suggest that the EEG of schizophrenics can be temporarily altered using feedback techniques, in a way that mimics the EEG changes that have been shown to occur with neuroleptic-induced clinical improvement.

Slow cortical potentials (SCPs) are considered to reflect the regulation of attention resources and cortical excitability in cortical neuronal networks. Impaired attentional functioning, as found in patients with schizophrenic disorders, may co-vary with impaired SCP regulation. In controlled studies on SCPs, neurofeedback treatment has shown improvement in cognitive functions in schizophrenia patients.[203–205]

In review articles[206,207] it has been concluded that in view of the affirmative evidence and advances in understanding the functional significance of EEG rhythms, the undertaking of therapeutic regimens with electrocortical operant conditioning is warranted in the schizophrenia spectrum. The positive findings using rTMS in schizophrenia,[208–210] where statistically significant decreases in AHs have been reported when the left temporoparietal cortex and left dorsolateral prefrontal cortex were stimulated, have raised the possibility that neurofeedback, which is a safer way to modulate brain activity, could be an alternative treatment option for schizophrenia.[211]

The effect of neurofeedback treatment for sleep problems in chronic schizophrenia patients has been shown in a controlled multiple case study only.[212] However, although neurofeedback has been extensively studied in the treatment of many disorders, there have been few published uncontrolled case reports on its clinical effects in the treatment of schizophrenia.[211,213]

In the paper by Sürmeli et al.[211] a group of 51 schizophrenic patients were treated with neurofeedback. In this study subjects with a PANSS total score of 70 or above were included (range: 76–156; between 70 and 79: two subjects; 80–89: nine subjects; 90–99: eight subjects; 100–109: five subjects; 110–119: nine subjects; 120–129: five subjects; 130–139: five subjects; and >140: five subjects). The results showed that 47 out of 48 participants showed clinical improvement after neurofeedback treatment, as indicated by changes in their PANSS scores, where the group's mean score of 110.24 (SD 21.62) decreased to 19.56 (SD 26.78). This change was found to be statistically significant. The participants who were able to take the Minnesota Multiphasic Personality Inventory (MMPI) and the Test of Variables of Attention (TOVA) showed significant improvements in these measures as well. Forty of the subjects were followed up for more than 22 months, two for 1 year, one for 9 months, and three for between 1 and 3 months after completion of neurofeedback. The average reduction in PANSS scores was 83% (SD 23), which was above the 20% change seen when only antipsychotic medications were used. In the study, 94% of the subjects complied with the

neurofeedback regimen, and of those who needed medication, 68% complied with their drug treatment when followed for up to 2 years. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, the efficacy of the pharmacological treatment on the primary measure, which was the subject staying in the study until completion, was only 26%.[214–216] In a study conducted by Schummer and von Stietz, after a patient was treated with neurofeedback to reduce his coherence abnormalities, his treatment dose of apiprazole was reduced from 20 mg to 7.5 mg, with an improvement of functioning giving him the ability to graduate from college.

When reading much of the literature on efficacy of various treatments with schizophrenic patients, it is useful to have information concerning the rating scales used.

The PANSS is the most commonly used clinical rating scale in registration trials of new antipsychotic medications.[217] Clinical trials testing the acute efficacy of antipsychotics ordinarily have certain thresholds for eligibility, such as a PANSS total score of at least 70 or 80 (although sometimes lower thresholds have been used). It is commonly observed that the baseline PANSS total score for participants in acute schizophrenia trials averages around 90, give or take 10 points. A PANSS total score of more than 120 would be considered very high and likely incompatible with being able to participate in a placebo-controlled clinical trial of monotherapy. Although mean change in PANSS total scores is often the primary outcome measure in a registration trial, it is more clinically relevant to know how many patients achieved a certain degree of improvement. A "responder analysis" can help address this, and inform the clinician about the proportion of patients who achieved a certain reduction in psychopathology, for example a 20% (barely perceptible), 30% (modest improvement) or 40% (relatively robust improvement) decrease in their PANSS total score from baseline. Clinically, it may be quite relevant to know that in a clinical trial 45% of the patients receiving the antipsychotic "responded," compared to 15% for placebo. This 30% difference in response rates would be considered attributable to the medication.[214,218,219]

The efficacy of the biofeedback treatment methods that have been used in schizophrenia likely falls into the range "possibly efficacious" to "probably efficacious" according to the guidelines jointly established by the Association for Applied Psychophysiology and Biofeedback and the International Society for Neurofeedback and Research (Table 9.1).[214]

Table 9.1 Published Studies on Biofeedback in Schizophrenia

Authors	Treatment Type	N	In/ outpatient	Controls/groups	Sessions	Outcome
Schnieder SJ, Pope AT. [202]	NF to mimic neuroleptic-induced EEG changes	9	Out	None	5	Significant within session changes. Not significant between session changes
Cortoos A, Verstraeten E, Joly J, et al. [212]	NF Effect of NF on sleep	13	In	NF Group Control group	40	Sleep quality improved
Bolea AS. [213]	NF Clinical study	1	In	None	130	Improvement in symptomatology and neuropsychological tests. Subject discharged to community living and improvements lasted for 2 years. NF was administered to more than 70 inpatients with chronic schizophrenia who had been hospitalized for as long as 20 years
Sürmeli T, Ertem, A, Eralp E, Kos, IH. [211]	NF Clinical study	51	Out	None	58,8 (average)	Statistically significant improvement in PANSS MMPI, TOVA, with improvements seen up to 2 year follow-up in majority of cases

Schneider F, Rockstroh B, Heimann H et al.[203]	SCP	12	In	12 Healthy controls	20	Difference with controls (poorer learning), however in the last 3 sessions no difference with controls
Hardman E, Gruzelier J, Cheesman K, et al. [204]	SCP Reducing left right asymmetry in slow potential negativity in F3, F4	16	Out	8 Coached to use emotional strategies, 8 no strategy	3	Significant learning in both groups
Gruzelier J, Hardman E, Wild J, Zaman R. [205]	SCP Reducing left right asymmetry in slow potential negativity in C3, C4	16	Out	None	10	Patients were able to learn and control interhemispheric asymmetry. Ratings of anxiety and tension on the positive and negative symptom scale were closely related to reduced performance. A follow-up examination of case studies revealed that one participant evidenced a 50% reduction on a global psychopathology score. Another participant evidenced EEG readings that suggested the prior conditioning had persisted over 3 months
Acosta FX, Yamamoto J. [195]	EMG Biofeedback	6	Out	None	10+	Reduced EMG

(*Continued*)

Table 9.1 (Continued)

Authors	Treatment Type	N	In/ outpatient	Controls/groups	Sessions	Outcome
Nigl AJ, Jackson B. [220]	EMG Biofeedback	10	In	2 Groups Normal controls	6	All groups significantly reduced level of muscle tension. Length of hospitalization decreased in group that received biofeedback
Weiner [196]	EMG Biofeedback	6	Out	None	Operant paradigm	Easier to increase than reduce EMG
Keating [197]	EMG Biofeedback	4	In	None	22	EMG reduced, anxiety reduced in 3 subjects
Pharr OM, Coursey RD. [194]	EMG Biofeedback (frontalis and forearm extensor muscles)	30	In	Randomly assigned to: progressive relaxation group control group	1 orientation 6 active	Tension–Anxiety Scale of the Profile Mood states – not significant Nurses' Observation Scale for Inpatient Evaluation – Social Competence and Social Interest Factors Significant Improvement
Hawkins RC 2nd, Doell SR, Lindseth P, et al. [199]	Thermal biofeedback and relaxation therapy	40	In	Randomly assigned to: biofeedback, relaxation, biofeedback and relaxation, and minimal treatment control	10	No between-group differences. One-year follow-up and post hoc analyses indicated a subgroup of "anxious" schizophrenics who showed substantial reduction in anxiety following treatment with biofeedback and relaxation
Stien F, Nicolic S. [192]	Stress management, including biofeedback	1	Out	None	7	Improvement of 7 out of 20 items of the State–Trait Anxiety Inventory

Finally, all of the studies of EEG biofeedback in schizophrenia to date have used EEG biofeedback as an add-on to antipsychotic treatment regimens, so any statements of efficacy would have to acknowledge that EEG biofeedback has not been used as a stand-alone treatment for schizophrenia.

The criteria for Levels of Evidence of Efficacy of levels 1–5 are as follows:

- **Level 1: Not empirically supported**. This classification is assigned to those treatments that have only been described and supported by anecdotal reports and/or case studies in non-peer-reviewed journals.
- **Level 2: Possibly efficacious**. This classification is considered appropriate for those treatments that have been investigated in at least one study that had sufficient statistical power and well-identified outcome measures, but lacked randomized assignment to a control condition internal to the study.
- **Level 3: Probably efficacious**. Treatment approaches that have been evaluated and shown to produce beneficial effects in multiple observational studies, clinical studies, wait-list control studies, and within-subject and between-subject replication studies merit this classification.
- **Level 4: Efficacious**. In order to be considered "efficacious", a treatment must meet the following criteria:
  - In a comparison with a no-treatment control group, alternative treatment group or sham (placebo) control group using randomized assignment, the investigational treatment is shown to be statistically significantly superior to the control condition, or the investigational treatment is equivalent to a treatment of established efficacy in a study with sufficient power to detect moderate differences.
  - The studies have been conducted with a population treated for a specific problem, for which inclusion criteria are delineated in a reliable, operationally defined manner.
  - The study used valid and clearly specified outcome measures related to the problem being treated.
  - The data are subjected to appropriate data analysis.
  - The diagnostic and treatment variables and procedures are clearly defined in a manner that permits replication of the study by independent researchers; and
  - The superiority or equivalence of the investigational treatment has been shown in at least two independent studies'.
- **Level 5: Efficacious and specific**. To meet the criteria for this classification, the treatment needs to be demonstrated to be statistically

> superior to a credible sham therapy, pill or bona fide treatment in at least two independent studies (LaVaque et al. 2002, p. 280).[221]

Example Case Study: This Case Study as an "Illustration" of neurofeedback Treatment

To end this chapter with an illustration of successful neurofeedback treatment, a case study is presented below.

A 27-year-old woman previously diagnosed with bipolar disorder and psychosis was treated for 4 years. Her symptoms started with some obsessive thoughts. Her problems included obsessions, hearing voices, communicating with people on the television, talking to herself out loud, laughing inappropriately, not getting pleasure from life, not being able to do housework, and not being able to attend her college classes. One of the psychiatrists from the local government hospital put her on depakote and olanzepine. She had four psychotic episodes while on medication, and her condition did not improve.

When she came to our center she was "washed out" of all medication in preparation for her qEEG recording. During the washout she became fully psychotic. However, her baseline qEEG was able to be recorded, medication-free. Based on her qEEG, the NxLink database suggested a diagnosis of schizophrenia (and not bipolar disorder), which was in agreement with the clinical judgment of the examining physician.

Here it is important to note that, although her illness could not be differentiated clinically between bipolar disorder and schizophrenia, her qEEG findings were able to suggest a similarity to the brain electrical activity seen in schizophrenia, and not that seen in bipolar disorder.[222]

After her psychotic episode, risperidone 3 mg/day was administered and her qEEG was re-recorded (Figure 9.1). Her psychotic episode, coupled with the medication, may have increased theta and theta hypercoherence.

Based on these findings, we decided to reduce theta and theta hypercoherence with neurofeedback. With this treatment regimen the obsessive thoughts and AHs disappeared, as did her talking to people via the TV. Her talking to herself and laughing inappropriately also disappeared. She functioned much better and was able to continue her college courses. These changes were observed clinically also. Her PANSS positive score decreased from 18 to 2, her negative score from 42 to 2, and her global scores from 90 to 2, reducing her total score from 150 to 60. Her MMPI results showed similar improvement. The schizophrenia scale T-score

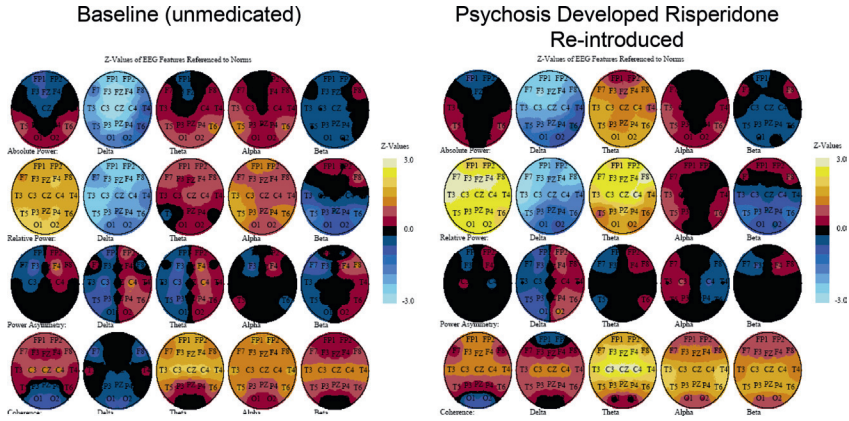

Figure 9.1 As can be seen, the psychotic episode increased theta activity. The coherence increase may be related to a drug effect or to the exacerbation of the illness. However, her baseline qEEG was able to be recorded, medication free.

decreased from 80 to 49. Other MMPI scores that showed improvement were psychasthenia T-score (81 to 44), psychopathic deviation T-score (79 to 40), paranoia T-score (74 to 45) and depression T-score (73 to 43). Following the treatment she functioned much better with only 2 mg risperidone per day and was stable for 2 years. After 2 years the patient was lost to follow-up.

CONCLUSIONS

The current treatment of choice for thought disorders is medication. However, a major drawback of pharmacological treatment is that this group is not very compliant with treatment. According to the CATIE study, about 74% of the schizophrenia patients who have discontinued the first medication prescribed will have a relapse within a year.[215]

There is a lack of studies investigating the efficacy of long-term drug treatment. Most studies are rarely longer than 12 weeks, and those that have looked into long-term use fail to show efficacy.[223] However, treatment periods with these drugs most often are longer than the durations that have been investigated by clinical studies. The currently available evidence does not provide enough information to predict which antipsychotic will provide the best treatment with the fewest side effects. Therefore, current drug selection involves a trial and error approach by the clinician.[206] Another issue is that a "one size fits all" treatment

approach (usually with antipsychotic medications) may not be beneficial for a particular patient population, and more personalized treatments may be needed.[211]

The idea of "personalized" treatment is consistent with subclusters of dysregulation indicated by qEEG analyses, but qEEG is not yet widely used.[1] Neurofeedback protocols derived from qEEG analyses enable a tailoring of treatment protocols to specific brain regions and their functional status in a more individualized manner than can currently be provided by medications.

The clinical studies with schizophrenia performed by Bolea[213] and Sürmeli et al.,[211] and studies done with OCD,[224] are limited in that they are not controlled or blinded. However, recent comparisons between randomized controlled studies and randomized observational studies have shown that there is no great difference in treatment effects between the two, and that observational studies do provide relevant treatment information.[225–228]

The evidence of the effectiveness of neurofeedback as a treatment modality for thought disorders is increasing. Although efficacy is being shown clinically and reported in clinical case series, there is a lack of placebo-controlled studies of treatment of thought disorders using neurofeedback. This may be a result of the difficulty of applying the "gold-standard" placebo control to neurofeedback. A first reason for this is that if the sham control is not designed properly, subjects usually are able to identify the sham treatment, thereby breaking the blinding.[229] A second factor is an ethical one. According to the Helsinki accords, sham or placebo-controlled studies are ethically acceptable only for those disorders for which no effective treatment is available. Therefore, an active treatment control group (treatment equivalence) design is most appropriate for those clinical studies examining disorders for which there is a known, effective treatment.[230] Relevant to this, the use of sham feedback (placebo) in evaluating the efficacy of neurofeedback in the ADHD population was declared unethical by the University of California, San Diego.[231] This being the case, successful controlled neurofeedback studies are being conducted where efficacy is being demonstrated by comparing neurofeedback results to those found in a control group treated by some other treatment known to be effective.[170] In the treatment of thought disorders, it follows that according to Helsinki criteria the appropriate studies would be comparing neurofeedback to drugs approved by the Food and Drug Administration for thought disorder (e.g., antipsychotics).

With the growing importance of personalized medicine, these types of treatments (such as neurofeedback) 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.*[232]

According to Elkins et al.,[233] among the most frequently used complementary and alternative therapies, biofeedback is substantial, with 30% use among psychiatric inpatients (9% of them schizophrenics). So, we may conclude that biofeedback has been gaining importance among psychiatric illnesses. This chapter ends with a quote from Lamb,[234] who noted that many schizophrenic patients are neglected because clinicians conclude that they have lost the ability to cope independently in a normal environment. Lamb continued: "If mental health professionals pursue goals and use techniques that are not consistent with clinical reality, the recently revived interest in the chronically mentally ill will be lost out of frustration, staff burnout, and the disappointed hope of the administrators and the general public" (p 1007).

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