Non-invasive brain stimulation is a complex network disorder in urgent need of novel treatments that are effective and well tolerated. Non-invasive brain stimulation has potential to address this need by restoring impaired network activity patterns associated with the symptoms of schizophrenia. Despite a surge in interest and in the number of (mostly small) trials, no specific paradigm has yet emerged as a game-changing treatment paradigm. Here, we review studies of transcranial magnetic stimulation, transcranial direct and alternating current stimulation, and electroconvulsive therapy. We discuss the current challenges and propose several key directions for research aimed at developing the next generation of non-invasive brain stimulation paradigms for the treatment of schizophrenia. In particular, we highlight the importance of measuring target engagement by the stimulation, developing novel stimulation waveforms by rational design, and performing larger, more definite multi-center clinical trials.

Non-invasive brain stimulation has seen a dramatic surge in interest and publications in the last two decades. Schizophrenia represents in many ways a particularly exciting application for non-invasive brain stimulation for several reasons. First, available antipsychotic medications are only partially effective and often have considerable tolerability problems. Second, schizophrenia can be characterized as a network disease; there is quite substantial albeit incomplete evidence that the symptoms of schizophrenia arise from altered network dynamics in local networks and from pathological changes in large-scale networks across the brain (Birur, et al. 2017; Uhlhaas and Singer, 2012).

Two main non-invasive brain stimulation approaches besides electroconvulsive therapy (ECT) have been investigated for schizophrenia. Transcranial magnetic stimulation (TMS) delivers superthreshold stimulation by application of a magnetic field that induces an electric field in the brain. TMS excels in terms of spatial specificity since the magnetic field does not propagate in the head the way electrical current does. Therefore, stimulation at specific coordinates in the brain can be accomplished, in particular in conjunction with neuronavigation that utilizes computer vision for precise spatial targeting by adjusting the position of the stimulation coil. The resulting electric field by TMS is sufficiently strong to trigger the firing of action potentials. Stimulation amplitude is typically referenced to the amount of stimulation required to elicit a motor response by stimulation of the hand area of motor cortex (i.e., motor threshold). The main parameters for defining the TMS dose are the stimulation amplitude of the individual pulses (relative to motor threshold), the stimulation frequency (often 10 Hz, mostly for historical reasons), the number of pulses per stimulation session and the number of sessions. In terms of spatial targeting, the stimulation
Transcranial direct current stimulation (tDCS) is a low-intensity electrical stimulation modality, which works by the application of weak electrical current by scalp electrodes (Nitsche and Paulus 2000). Despite the historical reports going back centuries of the application of constant current (in the language of electrical engineering: direct current), the field experienced a dramatic revival and expansion with several publications pointing to changes in motor cortex excitability after brief tDCS stimulation. Given the technical simplicity of tDCS (especially in comparison to TMS that requires quite complex hardware), this stimulation modality experienced rapid growth with numerous reports about seemingly positive effects on an uncountable number of brain targets, functions, and symptoms. The main parameters that define the tDCS dose are the current amplitude (typically 1–2 mA), the electrode size (often many square centimeters), the direction of the current (anodal versus cathodal), the duration of the stimulation session, and the number of sessions. In terms of spatial targeting, the stimulation location determined by the position of the stimulation electrodes is a key determinant of the effect of stimulation. Despite a growing research base, tDCS does not yet have FDA approval for any clinical indication. More recently, transcranial alternating current stimulation (tACS) has emerged as a noninvasive brain stimulation modality to modulate cortical brain rhythms measured by electroencephalogram (EEG). tACS is also applied by scalp electrodes but uses a sine-wave electric current typically with a predefined frequency to engage specific brain rhythms by entrainment (Ali, Sellers, and Frohlich 2013; Kanai et al. 2008).

As we discuss in this chapter, TMS, tDCS, and tACS have been investigated in people with schizophrenia. The growing literature has yet to provide clear answers in terms of therapeutic benefit. This should not surprise given the complexity of the illness and the likely multifactorial biological processes that lead to symptoms of schizophrenia. Given the heterogeneity of study designs, a systematic meta-analysis would provide a false sense of reassurance in the sense that the underlying literature has not yet reached the quality or quantity to justify global conclusions about efficacy. Rather, we highlight a series of studies that demonstrate the state of the field and provide an extensive discussion of the salient points that we argue should be considered by the field as we move forward with the next generation of studies. It is noted that hindsight is always 20/20 and we emphasize that shortcomings of early trials (including some performed by us) are not the result of poor scientific practices but rather a reflection of the limited knowledge available at the time to a nascent field of study. In addition, we note that when conducting clinical trials that enroll people with schizophrenia, some design choices are best understood in context of the specific clinical characteristics and functional limitations of this study population.

**Transcranial direct current stimulation**

tDCS has been investigated for several aspects of schizophrenia. A number of papers have been published on the use of tDCS (and tACS) for the treatment of auditory hallucinations in schizophrenia (and schizoaffective disorder). This line of research started with a case report of a person with schizophrenia who had medication–resistant auditory hallucinations (Homant et al. 2011). The patient received 15 minutes of tDCS for 10 days (1 mA, 7 cm x 5 cm electrodes). The cathode was positioned over Wernicke’s area and the anode was positioned over the right supraorbital area. An improvement in terms of hallucinations, positive and negative symptom scale (PANSS), and the psychotic symptom rating scale was reported. The symptom improvement was maintained six weeks after completion of the tDCS course. Intriguingly, measurement of blood flow by arterial spin labeling showed a decrease in cerebral blood flow in language areas. This first case report created an exciting starting point for the investigation of tDCS as a potential treatment for schizophrenia. While most subsequent studies have focused on the effects of tDCS on auditory hallucinations, the effects of tDCS has been assessed on all dimensions of psychosis. This chapter will review the tDCS literature on positive symptoms (including auditory hallucinations), negative symptoms and cognition.
Positive symptoms

Following the initial encouraging case report, a double-blind placebo-controlled trial in thirty patients with schizophrenia with medication-refractory auditory hallucinations was published that represents a hallmark study in the field (Brunelin et al. 2012). The study employed a double-blind design (placebo: “sham” stimulation) and a 20-minutes twice-per-day stimulation paradigm (2 mA). The cathode was positioned over left temporo-parietal cortex, whereas the anode was positioned over left dorsolateral prefrontal cortex. Not only was there a statistically significant and clinically meaningful reduction of auditory hallucinations (assessed using the Auditory Hallucination Rating Scale, (AHRS)) in comparison to the sham group immediately after the 5-day course of treatment, but the improvement persisted up through the final follow-up visit at 3 months. Given these compelling results, a number of studies were initiated to build on these findings. A subsequent pilot study that used similar (and bilateral) stimulation was negative (Fitzgerald et al. 2014). The authors list the difference in stimulation protocol as one of the main reasons that could explain the difference in outcomes between these two studies (daily for 3 weeks in their case, versus twice daily for 1 week). A study with a different electrode montage that targeted exclusively frontal cortex also found no improvement in auditory hallucinations (Smith et al. 2015). A frequently cited follow-up study (Mondino et al. 2015) appears to replicate the initial results from Brunelin and colleagues. It is noteworthy that more than half of the participants (15 out of 23) in the follow up report are the same as those in the initial study, which decreases the interpretability of the findings. A study by Frohlich and colleagues of once daily (20 min) tDCS for 1 week was also negative. This double-blind, randomized, placebo-controlled study included 26 patients (n = 13 active, n = 13 sham). This study found a qualitatively similar reduction in auditory hallucinations when compared to the original trial by Brunelin; however, the sham group also improved substantially and no between-group difference emerged (Fröhlich et al. 2016). These divergent findings put a spotlight on blinding procedures in such tDCS trials. Several subsequent studies have demonstrated significant improvement in persistent auditory hallucinations between verum and sham tDCS (Bose et al. 2018; Lindenmayer et al. 2019) while others have found no difference (Koops et al. 2018; Kantrowitz et al. 2019). In a follow-up study, Frohlich et al compared tDCS, tACS, placebo (sham stimulation), now employing the twice-daily paradigm. The study was not powered to detect statistically significant differences; yet effect size analysis pointed to a lack of efficacy of tDCS in comparison to tACS (Mellin et al. 2018). This study included comprehensive measures of target engagement by repeat high-density electroencephalography, which represent the first demonstration of successful modulation of cortical oscillations with tACS in a clinical stimulation paradigm (details to follow) (Ahn et al. 2019). The next tDCS trial included so far the highest number of participants (54) but failed to find any difference between tDCS and placebo (Koops et al. 2018). Similarly, yet another trial with 60 patients also failed to find a difference between verum and placebo stimulation (Chang et al. 2018). In contrast, a smaller study (28 patients) reported a small benefit of tDCS versus sham stimulation for a 4-week paradigm (Lindenmayer et al. 2019). In the largest study to date (89 participants), the primary outcome did not reach statistical significance. However, an exploratory analysis that covaried for total antipsychotic dose equivalents reached statistical significance. When considering all these double-blind placebo-controlled studies together, several aspects stand out that are worth considering.

One recent meta-analysis on the efficacy of tDCS in sham-controlled randomized trials identified five eligible studies (n = 143 participants) and showed a non-significant reduction (effect size = -0.28, p = 0.38) on auditory hallucination scores (Kennedy, Lee, and Frangou 2018). Similarly, another meta-analysis found that, among seven eligible studies (n = 242 participants), there was no significant effect of tDCS on auditory hallucinations in the main analysis (Kim et al. 2019). However, in a subgroup analysis that focused on studies that used twice-daily stimulation (four studies, n = 138 participants), tDCS was associated with a significant large reduction in auditory hallucinations (effect size = 1.04, p = 0.02). While studies using twice-daily stimulation are suggestive of efficacy, the sample sizes of these studies have been small. Furthermore, the durability of potential treatment effects has not been consistently examined in studies to date. One or more fully powered multi-site studies using a randomized, double-blind, sham-controlled design that includes a longer follow-up phase are needed to provide clarity on the question of tDCS efficacy for auditory hallucinations.

Clearly, tDCS is not a magic bullet for auditory hallucinations. Rather, like most interventions in psychiatry there are numerous factors, often seemingly minor during study design, that can profoundly impact the outcome. For example, the details of the study population may matter. These studies had different type of exclusion criteria for medication classes such as antiepileptic drugs often prescribed as mood stabilizers.
Also, schizophrenia represents in many ways a very global disease class and different subsets of patients may exhibit differing underlying circuit dysfunction that in turn determine the response to stimulation. For example, the latest study by Javitt and colleagues makes an argument that the degree of cognitive impairment impacts the response to stimulation, albeit no mechanism for this proposed interaction is proposed (Kantrowitz et al. 2019). All aspects of dose may matter. After the publication of the first few trials, it appeared that twice-daily stimulation was required for efficacy. In response, all studies switched to a twice-daily regimen, modeled after the original Brunelin and colleagues’ study (Brunelin et al. 2012). Yet, there is no clear rationale for this approach, it remains untested in a head-to-head trial, and patient burden is substantially increased by adding a break of three hours between the two stimulation sessions. Other aspects of dose that may matter are for example what patients are doing during stimulation. If tDCS modulates cortical excitability and plasticity of the targeted areas, the brain state during stimulation may determine the eventual outcome. We would like to argue that understanding these subtleties is required for reconciling the differing study outcomes. One way to address the divergences in the literature would be to perform a large fully powered multisite study as this approach would enforce a uniform approach to the specific stimulation protocol.

Finally, the key missing aspect in most of these studies is the demonstration of successful target engagement. Very few studies present any measures of changes in brain activity with stimulation. Plausibility of the effect of tDCS on auditory hallucinations in schizophrenia would be greatly enhanced if the studies demonstrated an a priori hypothesized change in brain activity that is specific to verum stimulation when contrasted to sham stimulation. Ultimately, the best demonstration of a causal role of stimulation is a significant correlation between changes in symptoms and changes in the target network activity pattern. One study showed changes in resting state fMRI functional connectivity between the left temporoparietal junction and left anterior cingulate cortex correlated with symptom improvement after 5 days of twice-daily tDCS (Mondino et al. 2015). One other study showed successful target engagement and correlation with improvement of auditory hallucinations using EEG (Ahn et al. 2019). Specifically, 10 Hz tACS (designed to reduce neuronal excitability and increase top-down control) enhanced alpha oscillations in contrast to tDCS and sham stimulation. This successful target engagement of alpha oscillations correlated with clinical improvement of the auditory hallucinations.

When considering the effects of tDCS on all types of positive symptoms (i.e., delusions, disorganization and hallucinations), the available data are more consistent. Based on recent meta-analyses, tDCS has not demonstrated any significant effects on positive symptoms (Kennedy, Lee, and Frangou 2018; Kim et al. 2019). The overall effect sizes were very small and subgroup analyses that considered once-daily versus twice-daily or only those studies that applied ten or more stimulations also found no effect of tDCS on positive symptoms (Kim et al. 2019).
**Negative symptoms**

The initial study by Brunelin et al. (2012) found that negative symptoms (as a secondary outcome) were significantly improved by twice-daily tDCS compared to sham stimulation (effect size = 1.07, p = 0.01). A small follow-up study demonstrated no effect of tDCS on negative symptoms (Fitzgerald et al. 2014). Based on the purported relationship between negative symptoms and prefrontal cortical hypoactivity, another small study used once daily anodal stimulation over left DLPFC and cathodal stimulation over right DLPFC for 10 days and found significant reduction in negative (Gomes et al. 2015). A subsequent study enrolled 20 negative symptom–predominant patients with schizophrenia and applied ten once daily treatments of tDCS or sham using a left DLPFC anode and right orbitofrontal cathode montage (Palm et al. 2016). This trial also found a significant effect of tDCS compared to sham stimulation for negative symptoms, with significant benefits persisting at a 2-week post-treatment follow-up. As with the effect of tDCS on auditory hallucinations, subsequent studies have reported mixed outcomes. The most recent meta-analysis to examine the efficacy of tDCS on negative symptoms identified nine eligible studies (n = 313 participants) and found no main effect of tDCS on negative symptom severity (effect size = 0.27, p = 0.14) (Kim et al. 2019). Subgroup analysis of studies that used once-daily or twice-daily stimulation, or bi-frontal electrode placement also revealed no effect of tDCS on negative symptoms. Notably, another recent meta-analysis identified seven eligible studies (n = 190 participants) demonstrated a significant, moderate effect of tDCS on negative symptoms (effect size = -0.63, p = 0.02) (Kennedy, Lee, and Frangou 2018; Kim et al. 2019). Taken together, these data are suggestive but inconclusive on the efficacy of tDCS on negative symptoms. Future adequately powered studies will be required to better understand the potential benefits of tDCS for this recalcitrant symptom dimension of schizophrenia.

**Cognition**

Antipsychotic medications provide little if any cognitive benefit and among the myriad pharmacological agents with novel mechanisms of action that have been tested for possible pro-cognitive effects, no agent has proven effective in Phase 3 studies. Given this therapeutic gap, significant interest has emerged in exploring tDCS for cognitive dysfunction in schizophrenia. Single-session anodal stimulation over left DLPFC in a sham controlled, single-blind cross-over trial in 20 patients with schizophrenia showed no benefit on a probabilistic learning task in the overall cohort (Vercammen et al. 2011). However, post-hoc analysis revealed a subgroup of 12 participants with good learning capacity at baseline who demonstrated significant improvement with tDCS compared to sham. In another study, 18 patients with schizophrenia were randomized to receive anodal stimulation over left DLPFC (1 mA, 2 mA, and sham; each experimental session spaced by at least 72 hours) (Hoy et al. 2014). Participants performed a 2-back working memory task at 0, 20, and 40 minutes post-stimulation, showing significant improvement in working memory in the 2-mA arm compared to sham and 1 mA (Hoy et al. 2014). In a preliminary study exploring the effects of tDCS on social cognition, 36 patients with schizophrenia were randomized to single dose administration of anodal, cathodal or sham tDCS (12 randomized to each condition). The group that received anodal stimulation showed significant improvement in the emotion identification task compared to sham, although this finding did not replicate in a follow-up study (Rassovsky et al. 2015; Rassovsky et al. 2018).

A number of multi-session studies, most having applied anodal stimulation over left DLPFC and cathodal stimulation over right orbitofrontal cortex, have demonstrated signals of pro-cognitive effects. For example, Smith et al. (2015) conducted a randomized double-blind, sham controlled study of the effects of five daily sessions of tDCS on cognition, with the MATRICS Consensus Cognitive Battery (MCCB) as the primary outcome measure (Smith et al. 2015). Active tDCS showed significant improvement in MCCB composite score (effect size = 1.03, p = 0.008), as well as the working memory (effect size = 1.25, p = 0.002) and attention–vigilance (effect size = 0.84, p = 0.027) subscales. In 28 patients with schizophrenia who received 20 stimulation sessions, Lindenmayer et al. (2019) found no change in the overall MCCB composite score but identified a significant improvement in the working memory subscale with active tDCS compared to sham. Similarly, in 56 patients with schizophrenia who received ten stimulation sessions, MCCB composite score and working memory subscale improved significantly in tDCS compared to sham (Jeon et al. 2018). However, other studies have found no cognitive benefits of tDCS. For example, in 20 patients with negative symptom–predominant schizophrenia, working memory, processing speed and executive functioning were assessed as secondary outcome measures and all were unchanged after ten sessions of tDCS compared to sham (Palm et al. 2016). Several other double-blind, randomized, multi-session sham-
Positive symptoms

controlled trials have found no cognitive benefits of tDCS compared to sham (Koops et al. 2018; Chang et al. 2020).

Although the available data on the effects of tDCS on cognitive function are based on small sample sizes and substantial variability in terms of study designs, some signals have emerged suggesting that tDCS may have pro-cognitive effects in patients with schizophrenia. These conclusions are generally consistent with a meta-analysis from 2017 which identified six eligible studies and found that small positive effects were associated with anodal stimulation on measures of working memory and attention and marginal benefits on global cognitive functioning (Mervis et al. 2017). Larger studies that include markers of target engagement will be required to gain a better understanding of the potential pro-cognitive effects of tDCS in patients with schizophrenia.

With few studies to date having employed measures of target engagement, i.e., measure of change in brain activity patterns, it is difficult to draw firm conclusions about the relative efficacy of different stimulation protocols. We further emphasize that the numerous published case reports are of limited value given the pronounced placebo response in several of the well-controlled trials discussed previously. Additionally, there are numerous recently published meta-analyses that are based on the few available studies. We argue that the results of meta-analyses in a nascent field with small sample sizes is more likely to increase uncertainty rather than provide clarity. Finally, it may be worth mentioning that tDCS can be prescribed off-label in the US (using an FDA-cleared iontophoresis device). Despite the confusion in the scientific literature, we recognize a role for the case-by-case considerations of a tDCS empirical trial in individual, severely ill, treatment-resistant patients until double-blind placebo-controlled studies provide more insight.

Repetitive transcranial magnetic stimulation

Positive symptoms

Auditory hallucinations are frequently reported in patients with schizophrenia and these symptoms are refractory to antipsychotic medications in at least 25% of patients (Shergill et al., 1998). The earliest studies of rTMS in patients with schizophrenia examined its efficacy for auditory hallucinations. Twenty-four patients with schizophrenia or schizoaffective disorder with medication-resistant auditory hallucinations were randomized to receive once daily 1 Hz rTMS (n = 12) or sham stimulation (n = 12) over 9 days over the left temporoparietal junction (Hoffman et al. 2003). rTMS showed a significant effect on the Hallucination Change Scale (HCS) compared to sham. In a subsequent paper, Hoffman et al. (2005) reported on the combined cohort of the original 24 subjects (Hoffman et al., 2003) together with an additional 26 subjects (Hoffman et al. 2005). This report continued to show significant improvement on the HCS for rTMS compared to sham. Secondary outcomes included the Auditory Hallucination Rating Scale (AHRS) which showed significant reduction in the frequency of hallucinations with rTMS compared to sham but no differences on the other six dimensions of the scale and the composite AHRS score did not reach statistical significance. rTMS also did not differentiate from sham on the Positive and Negative Syndrome Scale (PANSS) positive symptom subscale (Hoffman et al. 2005).

Following the early reports of efficacy of rTMS for auditory hallucinations in schizophrenia, a number of subsequent sham-controlled randomized studies have examined this issue. Some trials found a benefit of rTMS for auditory hallucinations (Brunelin et al. 2006; Hoffman et al. 2013; Klirova et al. 2013), although many found no effect (Blumberger et al. 2012; de Jesus et al. 2011; Fitzgerald et al. 2005; Kimura et al. 2016; Koops et al. 2016; Lee et al. 2005; Slotema et al. 2011; Vercammen et al. 2009). A recent meta-analysis identified 14 studies with 340 patients who received rTMS and 238 patients who received sham stimulation (Kennedy, Lee, and Frangou 2018). The AHRS outcome measure demonstrated a significant effect of rTMS treatment (Hedge’s g = −0.51) on auditory hallucinations (Kennedy, Lee, and Frangou 2018). This result is consistent with another meta-analysis that reported an effect size = −0.29 for auditory hallucination improvement with rTMS over sham (He et al. 2017). However, He et al. (2017) also graded the quality of the meta-analytic evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methods proposed by the World Health Organization for producing practice guidelines (Guyatt et al. 2008) and determined that the overall quality of evidence was low, based on high levels of heterogeneity among studies, instability of the results due to substantial impact of single studies, as well as...
In a meta-analysis, Kennedy et al. (2018) also examined the impact of rTMS on all positive symptoms, not just auditory hallucinations. The authors identified 22 studies that reported PANSS positive symptom subscale scores in 585 patients who received rTMS and 414 patients who received sham and found no significant effect of treatment (Hedge’s g = 0.28). Notably, the direction of change, although not statistically significant, indicated that rTMS may be associated with worsening of positive symptoms (Kennedy, Lee, and Frangou 2018). This was further supported by associations between higher positive symptom scores and high frequency stimulation (over 20 Hz) (Hedge’s g = 0.64), 110% motor threshold intensity (Hedge’s g = 1.13), trials lasting over 3 weeks (Hedge’s g = 0.70) and treatment site over prefrontal cortex (Hedge’s g = 0.84). In another recent small meta-analysis that specifically analyzed the efficacy of rTMS in clozapine-refractory schizophrenia, the authors found no benefit of rTMS for positive symptoms in three studies involving 26 patients who received rTMS and 28 who received sham (Siskind et al. 2019). Although not amenable to meta-analysis, two of the studies reported no significant effect of rTMS on auditory hallucinations in clozapine-resistant patients (de Jesus et al. 2011; Rosa et al. 2007). Taken together, available data temper enthusiasm for broad applicability of rTMS for management of medication-refractory auditory hallucinations. Future well-designed and adequately powered studies will need to confirm efficacy of rTMS for auditory hallucinations without causing inadvertent exacerbation of other positive symptoms.

Negative symptoms

There is no evidence that antipsychotic medications demonstrate efficacy for primary or persistent negative symptoms (Buchanan et al. 2010). Given the recalcitrance of negative symptoms to antipsychotic medication treatment and the fact that the severity of negative symptoms is strongly associated with poor outcome, significant interest has emerged from several meta-analyses that have identified a positive therapeutic signal with rTMS for negative symptoms in patients with schizophrenia (Kennedy, Lee, and Frangou 2018; Freitas, Fregni, and Pascual-Leone 2009; Prikryl and Kucerova 2013; Shi et al. 2014). Most rTMS trials designed to test the effect on negative symptoms applied stimulation to left prefrontal cortex (PFC) at 10 Hz or greater (Kennedy, Lee, and Frangou 2018). The most recent meta-analysis showed a significant effect of treatment (Hedge’s g = −0.49), with additional associations for greater symptom response with older age, use of pulse frequency of 20–50 Hz, motor threshold intensity of 110%, trial duration > 3 weeks, and treatment site over the left PFC (Kennedy, Lee, and Frangou 2018). However, tempering these meta-analytic findings are the results of the only fully powered multicenter trial designed to test the hypothesis that left prefrontal rTMS is effective for negative symptoms in schizophrenia (Wobrock et al. 2015). In this trial, patients with schizophrenia selected for predominant negative symptoms were randomized to 10 Hz rTMS (n = 76) or sham stimulation (n = 81) applied to left PFC for 5 days per week for 3 consecutive weeks. The primary outcome, PANSS negative symptom subscale, showed no difference between active and sham groups (effect size = 0.09). The results of this rigorously conducted fully-powered study stands in contrast to the findings from multiple meta-analyses that suggested a benefit of rTMS using data from many underpowered studies, including a number of uncontrolled trials. The importance of considering the quality of the individual studies to which meta-analysis is being applied has been discussed previously and represents a critical consideration when trying to understand the impact of any intervention in a complex disorder such as schizophrenia.
Cognitive symptoms

Cognitive deficits in schizophrenia are substantial, they represent important determinants of overall functional outcome, and they remain inadequately treated by all available antipsychotic medications. Cognitive assessments have been conducted in many rTMS trials involving patients with schizophrenia, both to assess for possible cognitive-impairing effects and for possible cognitive benefits. Importantly, no evidence has emerged to indicate that rTMS is associated with detrimental cognitive effects (Blumberger et al. 2012; Fitzgerald et al. 2005; Rabany, Deutsch, and Levkovitz 2014; Dlabac-de Lange et al. 2015), a concern long associated with ECT (Lisanby et al. 2000). On the other hand, there is also little evidence to suggest that rTMS provides cognitive enhancement as measured across a broad range of cognitive domains (Hoffman et al. 2005; Blumberger et al. 2012; Fitzgerald et al. 2005; Rabany, Deutsch, and Levkovitz 2014). One small trial found an improvement in a test of semantic verbal fluency in the rTMS group compared to sham, but other cognitive assessments including processing speed and tests of memory and executive functioning showed no effect (Dlabac-de Lange et al. 2015). In the largest rTMS trial to date for schizophrenia, patients were selected for predominant negative symptoms and received left prefrontal 10 Hz rTMS or sham (Wobrock et al. 2015). Processing speed and executive function was assessed using the Trail Making Test A and B (Tombaugh 2004). The rTMS group showed a small but significant improvement in the Trails A but not Trails B measure, and it was judged to likely represent a practice effect rather than a treatment effect (Wobrock et al. 2015). In summary, rTMS does not appear to be associated with adverse cognitive effects nor provide meaningful cognitive benefits to patients with schizophrenia.

Electroconvulsive therapy

ECT represents a generally safe and well-established treatment for several serious psychiatric conditions including severe depression, mania and catatonia. ECT was first used as a treatment for schizophrenia in the 1930s, and early results appeared promising (Rudorfer, Henry, and Sackheim 2003). However, with the advent of antipsychotic medications in the 1950s and results from several studies showing comparable efficacy between ECT and antipsychotic medication treatment, interest in ECT for psychotic disorders waned considerably for several decades (Ali et al. 2019). In the 1970s, growing awareness of the therapeutic limitations of antipsychotic medications brought renewed interest in exploring the potential efficacy of ECT for schizophrenia. Overall, few high-quality trials have examined the efficacy of ECT in schizophrenia. Here, we review randomized trials that compared ECT versus sham ECT in people with schizophrenia. Almost all randomized ECT trials have been conducted in patients already receiving stable doses of antipsychotic medications. From a severity of illness perspective, investigators have focused on two patient types: those who meet treatment-resistant schizophrenia (TRS) criteria and those not specifically selected on the basis of illness severity. We will review these two groups separately.

Treatment-resistant schizophrenia

Key aspects of recently published consensus guideline criteria define TRS as patients with schizophrenia who show inadequate antipsychotic response (persistent psychosis with at least moderate functional impairment) over at least a 3-month duration and that patients have had two or more antipsychotic medication trials, each of sufficient dose (> 600 mg chlorpromazine equivalents per day) and duration (> 6 weeks at a therapeutic dose) (Howes et al. 2017). In clinical practice, TRS criteria are most often used for determining whether a patient is appropriate for a trial of clozapine, the only antipsychotic specifically approved for TRS. One of the greatest therapeutic challenges are those patients who meet TRS criteria and also fail to improve with clozapine.

Although very few clinical trials have studied ECT for clozapine-resistant patients, one well-designed prospective randomized trial demonstrated efficacy of ECT for positive symptoms and overall clinical functioning in patients with TRS and clozapine resistant symptoms (Petrides et al. 2015). In this trial, 39 subjects were randomized to clozapine with unilateral ECT (n = 20) or clozapine without ECT (n = 19). ECT was administered three times per week for the first 4 weeks, then twice weekly for the next 4 weeks. At the end of 8 weeks, 50% of subjects in the ECT augmentation group and 0% of subjects in the clozapine group met a priori response criteria (40% reduction in the positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS), a Clinical Global Impression (CGI)–Severity rating of mild or less and a CGI–Improvement rating of much improved or better). Notably, there were no differences in outcome on other cognitive assessments including processing speed and tests of memory and executive functioning. In summary, ECT represents a generally safe and well-established treatment for several serious psychiatric conditions including severe depression, mania and catatonia. ECT was first used as a treatment for schizophrenia in the 1930s, and early results appeared promising (Rudorfer, Henry, and Sackheim 2003). However, with the advent of antipsychotic medications in the 1950s and results from several studies showing comparable efficacy between ECT and antipsychotic medication treatment, interest in ECT for psychotic disorders waned considerably for several decades (Ali et al. 2019). In the 1970s, growing awareness of the therapeutic limitations of antipsychotic medications brought renewed interest in exploring the potential efficacy of ECT for schizophrenia. Overall, few high-quality trials have examined the efficacy of ECT in schizophrenia. Here, we review randomized trials that compared ECT versus sham ECT in people with schizophrenia. Almost all randomized ECT trials have been conducted in patients already receiving stable doses of antipsychotic medications. From a severity of illness perspective, investigators have focused on two patient types: those who meet treatment-resistant schizophrenia (TRS) criteria and those not specifically selected on the basis of illness severity. We will review these two groups separately.

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Although very few clinical trials have studied ECT for clozapine-resistant patients, one well-designed prospective randomized trial demonstrated efficacy of ECT for positive symptoms and overall clinical functioning in patients with TRS and clozapine resistant symptoms (Petrides et al. 2015). In this trial, 39 subjects were randomized to clozapine with unilateral ECT (n = 20) or clozapine without ECT (n = 19). ECT was administered three times per week for the first 4 weeks, then twice weekly for the next 4 weeks. At the end of 8 weeks, 50% of subjects in the ECT augmentation group and 0% of subjects in the clozapine group met a priori response criteria (40% reduction in the positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS), a Clinical Global Impression (CGI)–Severity rating of mild or less and a CGI–Improvement rating of much improved or better). Notably, there were no differences in outcome on other cognitive assessments including processing speed and tests of memory and executive functioning. In summary, rTMS does not appear to be associated with adverse cognitive effects nor provide meaningful cognitive benefits to patients with schizophrenia.
negative symptom ratings and no differences in global neurocognitive measures between the two groups. In a subsequent crossover phase for non-responders in the clozapine without ECT group, subjects received an 8-week open trial of ECT. Forty-seven percent (nine of 19) of these clozapine non-responders met response criteria to ECT in the crossover phase. While this trial is limited by a relatively small sample size and the lack of follow-up assessments, the results support the use of ECT for patients with clozapine-resistant TRS. This is also supported by a meta-analysis of studies of clozapine augmentation with ECT in TRS (Lally et al. 2016). Future studies should test both the durability of response following ECT discontinuation and the potential role of maintenance ECT in clozapine-resistant TRS.

Two other less rigorous randomized trials also provide support for ECT in TRS. In one small study, patients with TRS who were taking stable doses of chlorpromazine were randomized to receive six bilateral ECT treatments or sham (anesthesia without seizure induction) (Goswami, Kumar, and Singh 2003). BPRS scores improved significantly in the ECT group (n = 15) while the sham group (n = 10) showed no effect. CGI ratings did not change in either group. An important limitation was that only a completer analysis was presented. In another trial, 18 patients with TRS were assigned to one of three groups: ECT with clozapine, ECT with placebo, or clozapine with sham ECT (anesthesia without seizure induction) (Masoudzadeh and Khalilian 2007). Twelve unilateral ECT treatments were administered (three treatments per week for 4 weeks). Across the 12-week trial, total PANSS scores were significantly reduced by 71% in the combination group (ECT + clozapine), 40% in the ECT + placebo group and 46% in the clozapine + sham ECT group. For the PANSS positive subscale, significant symptom reductions were seen in the combination group and ECT + placebo group, while the clozapine + sham ECT group did not show significant change compared to baseline.

Non-treatment-resistant schizophrenia

Most studies of ECT in patients with schizophrenia, especially prior to the advent of clozapine, did not distinguish patients on the basis of treatment resistance. A recent systematic review identified seven trials in which patients with schizophrenia who were taking stable doses of first-generation antipsychotic medications were randomly assigned to receive ECT or sham (Ali et al. 2019). The majority of these trials demonstrated no effect of ECT on positive symptoms of psychosis as measured by the BPRS scale (Sarkar, P., et al. 1994; Ukpong, Makanjuola, and Morakinyo 2002; Agarwal and Winny 1985; Sarita et al. 1998). Three earlier studies found significant improvement with ECT on symptoms of psychosis compared to sham (Taylor and Fleminger 1980; Brandon et al. 1985; Abraham, and Kulhara 1987). For example, Taylor and Fleminger (1980) randomized 20 patients to receive 8–12 ECT treatments or sham over a 4-week period with follow-up assessments at 4 and 12 weeks after the end of treatment. Symptoms were reduced by ~ 50% in the ECT group compared to sham at end of the 4-week treatment period. However, while the benefits appeared to plateau in the ECT group by the end of the treatment period, the sham group continued to improve beyond the end of treatment and the intergroup difference lost statistical significance in all follow-up assessments (Taylor and Fleminger 1980). Similar loss of significant statistical effect between ECT and sham groups in follow-up assessments was observed in the other two positive ECT trials (Brandon et al. 1985; Abraham and Kulhara 1987).

Conclusions

Although the available research on the use of ECT in patients with schizophrenia is limited, several conclusions can be made: 1) The strongest evidence for use of ECT in schizophrenia is for those patients with clozapine-resistance, 2) ECT in non-clozapine TRS is suggestive of efficacy, 3) Some people with schizophrenia who do not have TRS may benefit from ECT but the majority of studies find no benefit and in those studies where benefit was identified, it was uniformly transient, 4) Additional research with prospectively randomized trials is clearly needed to confirm the benefits of ECT in people with clozapine-resistant schizophrenia, a patient population with few realistic treatment options and for whom their illness exerts a tremendous daily toll on their lives.
Next steps

Despite the heterogeneity of outcomes across studies, it seems fair to state that there is sufficient evidence for potential efficacy justifying further investigations. The field is encouraged to learn the lessons from this initial wave of enthusiasm and to move forward with the design and evaluation of the next generation of stimulation paradigms. One striking feature of the literature discussed in this chapter is the limited diversity of waveforms investigated. The field has mostly locked in on few basic stimulation paradigms that have been recycled again and again. This would not be a concern if it were not for the fact that the resulting plethora of small studies have failed to provide conclusive answers. We thus envision the following next steps for our field. First, the standard paradigms should be tested in large, multicenter studies. These studies will be costly but would provide conclusive answers for the first generation of stimulation paradigms such as tDCS, 10 Hz–tACS, and 10 Hz rTMS. It may even be worth contrasting these paradigms in one integrated study performed by a consortium. Second, the field must break free from these basic waveforms and start to leverage the unique advantage of brain stimulation: the fact that there are an infinite number of different stimulation waveforms and protocols that could be used. It is almost a given that a constant current or an artificial, purely periodic waveform (pulses in the case of rTMS or sine-wave in the case of tACS) does not represent the ideal stimulation strategy to engage brain network dynamics that exhibit numerous features beyond the basic descriptors such as specific oscillation peaks and neuronal activity level measured by fMRI (Cole and Voytek 2017). We will now expand on these two overall recommendations.

Rigorous multicenter studies

Overall, brain stimulation studies differ from studies of neuropharmacological agents in terms of the relative ease of implementation and execution. Once equipment is available, there are few hurdles to prevent active enrollment, assuming access to clinical populations. Overall, this relative ease of implementation enables new and creative research and represents a strength of the methodology. However, an unwanted consequence is the exuberant proliferation of numerous small and inconclusive studies. Today is the time to focus on collaboration and to convince funding agencies that we desperately need rigorous multisite studies to ensure that the lack of enthusiasm that often follows initial hype around novel treatments does not decimate the field before it has sufficiently matured. The details of such a study design would need to be developed by a consortium. Most importantly, the study should be adequately powered and include appropriate blinding and control participants. Measurement of target engagement (e.g., EEG, fMRI) is critical for ensuring that knowledge is advanced with each new study in order to best refine and improve the stimulation modality.
Novel stimulation paradigms

Stimulation waveforms and stimulation paradigms in general that are more targeted represent the next step. For this to be successful, clinical scientists need to collaborate with basic scientists who study network functional interactions and mechanisms of brain stimulation. Novel insights about brain network dynamics should be used to develop new stimulation paradigms (Kurmann et al. 2018). Individualization of stimulation to the specific patient may dramatically improve target engagement and perhaps even clinical response. Many aspects of the stimulation paradigm could be individualized (with some variations between stimulation modalities): stimulation location, stimulation intensity, stimulation waveform (e.g., tuning to individual stimulation frequencies), and many more. Beyond such individualization, stimulation could also be adaptive such that based on measured brain state, a different stimulation waveform is applied (Thut et al. 2017). Such feedback stimulation was, for example, used for targeting sleep spindles with tACS in healthy participants (Lustenberger et al. 2016). In addition, mechanism of potential synergies between pharmacology and stimulation should be explored. For example, little is known whether and/or how antipsychotics modulate the response to stimulation. In fact, even behavioral treatment strategies may be amplified in their therapeutic efficacy by smart integration with non-invasive brain stimulation. Such a rational design approach is hampered by the fact that there is no generally accepted animal model of schizophrenia to explore the underlying mechanisms of action. Rather, there are different models of specific genetic and neurobiological features that are shared with schizophrenia. Pharmacological dissection of putative pathophysiological and therapeutic mechanisms has been underway for decades. It is time to start investigating brain stimulation in such animal models of altered structural and functional connectivity and to use today’s advanced machine learning paradigms to extract the relevant stimulation features and to design optimized stimulation waveforms to restore and enhance the activity patterns underlying the symptoms of schizophrenia.

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