Brain Stimulation and Group Therapy to Improve Gesture and Social Skills in Schizophrenia—The Study Protocol of a Randomized, Sham-Controlled, Three-Arm, Double-Blind Trial

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An important component of nonverbal communication is gesture performance, which is strongly impaired in 2/3 of patients with schizophrenia. Gesture deficits in schizophrenia are linked to poor social functioning and reduced quality of life. Therefore, interventions that can help alleviate these deficits in schizophrenia are crucial. Here, we describe an ongoing randomized, double-blind 3-arm, sham-controlled trial that combines two interventions to reduce gesture deficits in schizophrenia patients. The combined interventions are continuous theta burst stimulation (cTBS) and social cognitive remediation therapy (SCRT). We will randomize 72 patients with schizophrenia spectrum disorders in three different groups of 24 patients. The first group will receive real cTBS and real SCRT, the second group will receive sham cTBS and real SCRT, and finally the third group will receive sham SCRT. Here, the sham treatments are, as per definition, inactive interventions that mimic as closely as possible the real treatments (similar to placebo). In addition, 24 age- and gender-matched controls with no interventions will be added for comparison. Measures of nonverbal communication, social cognition, and multimodal brain imaging will be applied at baseline and after intervention. The main research aim of this project will be to test whether the combination of cTBS and SCRT improves gesture performance and social functioning in schizophrenia patients more than standalone cTBS, SCRT or sham psychotherapy. We hypothesize that the patient group receiving the combined interventions will be superior in improving gesture performance.

Clinical Trial Registration: [www.ClinicalTrials.gov], identifier [NCT04106427].

Keywords: communication, social cognition, psychosis, theta burst stimulation, transcranial magnetic stimulation, intervention, cognitive remediation, schizophrenia

Abbreviations: ASL, arterial spin labeling; BOLD, blood-oxygen-level-dependent imaging; CBTp, Cognitive Behavioral Therapy for Psychosis; cTBS: continuous theta burst stimulation; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; IFG, inferior frontal gyrus, iTBS, intermittent theta burst stimulation; IPL, inferior parietal lobule; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; MRI, magnetic resonance imaging; PKT, postural knowledge test; PLD, point-light-display; PONS, profile of nonverbal sensitivity; RCT, randomized controlled trial; rIPL, right inferior parietal lobule; rTMS, repetitive transcranial magnetic stimulation; SCRT, social cognitive remediation therapy; SMA, supplementary motor area; TULIA, Test of upper limb apraxia.
INTRODUCTION

Schizophrenia is characterized by negative (e.g., affective flattening, avolition, low social drive) and positive symptoms (e.g., hallucinations, agitation, delusions) (1–3), as well as, disorganized thinking (4), motor abnormalities (5–7), and impaired cognitive function (8, 9). Social cognition, which refers to psychological processes that allow for the decoding of the behaviors and intentions of others (10–12), is also impaired in schizophrenia (13). In fact, impaired nonverbal communication is a core characteristic of social cognition deficits in patients with schizophrenia. Impaired nonverbal communication in schizophrenia includes limited nonverbal social perception (14–16) and poor gesture performance (17–19). Most importantly, gesture deficits are directly associated with patients’ poor functional outcome (20). This association between gesturing and functioning is the main reason why we believe that establishing treatments, which alleviate gesture deficits are essential to improve patients’ overall functioning and quality of life (21). Such treatments can potentially facilitate societal participation. With the current trial, we want to determine whether combined brain stimulation and group therapy improve schizophrenia patients’ gesture skills and social functioning.

Gesture Deficits in Schizophrenia

Gestures are an integral feature of communication: they support language production and transmit information on their own (22). Gesture deficits are prevalent in approximately two-thirds of patients with schizophrenia (17, 18, 23). Accumulating evidence suggests that various domains of gesturing are impaired in schizophrenia, including use of gestures (17, 18, 24, 25) and gesture perception (26). In fact, individuals with schizophrenia often use incoherent and fewer gestures (17, 27, 28) and tend to interpret gestures negatively (29, 30).

Gesture deficits in patients are associated with core schizophrenia symptoms, e.g., negative symptoms (24, 27), frontal lobe dysfunction (17, 18), formal thought disorder (23, 31) and working memory impairments (15, 24). At a neural level, gesture processing involves the praxis network, which combines motor- and speech-related brain areas (32, 33). Neuroimaging demonstrated structural and functional alterations in the praxis network in schizophrenia patients with gesture deficits (34–38). Specifically, two areas of the praxis network are linked to gesture deficits in schizophrenia: the inferior parietal lobule (IPL) and the inferior frontal gyrus (IFG) (39, 40). The IPL has been related to motor functioning, as well as cognitive and visuospatial processing (41–43). The IFG has been associated with motor functioning and language production (44).

Interventions Improving Gesture and Social Skills

Brain Stimulation

Repetitive transcranial magnetic stimulation (rTMS) has the potential to (re-)train distinct neural pathways and therefore rehabilitate specific functions in multiple neuropsychiatric disorders (45). Recent studies demonstrated rTMS efficacy across different domains in patients with schizophrenia. For example, rTMS over the supplementary motor area (SMA) ameliorated motor abnormalities (46, 47) and rTMS over the inferior parietal lobe (IPL) improved gesture performance (48). Different rTMS protocols can have different effects on brain function, depending on their frequency and type of stimulation (49).

Theta burst stimulation (TBS) is an innovative rTMS protocol, which requires less time than standard rTMS. There are two types of TBS: intermittent theta burst stimulation (iTBS), which mainly has facilitatory effects and continuous theta burst stimulation (cTBS), which has inhibitory effects. A pilot study demonstrated that inhibitory cTBS over the right inferior parietal lobe (rIPL) improved gesture performance by comparing 3 rTMS protocols (including sham stimulation) in 20 patients (48). Due to interhemispheric rivalry, cTBS on the right IPL may induce a facilitatory effect on left IPL through transcallosal disinhibition (50). As such, inhibitory cTBS over the rIPL is a promising method to reduce gesture deficits in schizophrenia. We decided to use the same cTBS protocol for repetitive administration in a larger sample.

Social Cognitive Remediation Therapy

Social cognition is a main driver of recovery and functional outcomes (10, 51–53) and mediates the relationship between neurocognition and social functioning in schizophrenia (53). The MATRICS initiative (Measurement and Treatment Research to Improve Cognition in Schizophrenia) of the National Institute of Mental Health (NIMH) identified the most important cognitive domains in schizophrenia (10, 54). These consist of six neurocognitive domains: speed of processing (1), attention/vigilance (2), working memory (3), verbal learning (4), visual learning (5) and reasoning/problem solving (6) and five social-cognitive domains: emotion processing (1), social perception (2), theory of mind (3), social schemata/knowledge (4) and social attribution styles (5). Therapies focusing on both neurocognition and social cognition are suggested to be a promising approach to help patients with schizophrenia (55–57).

One of the few integrative cognitive remediation therapies (CRT) covering all MATRICS domains is the Integrated Neurocognitive Therapy (INT) (58, 59). This CRT approach takes place in a group setting, including social interactive tasks and computerized neurocognitive exercises (using the Cogpack program). INT showed good feasibility with reduction of positive symptoms, negative symptoms and relapses, as well as, improvements in social cognition, neurocognition, and overall functioning in patients with schizophrenia (56, 60–62). The INT includes four modules, each addressing various cognitive domains: processing speed, attention, and perception of emotions (1); verbal and visual learning, memory, social perception, and theory of mind (2); reasoning, problem solving, and social schema (3); working memory and the ability to attribute appropriate meanings (4). INT focuses on the improvement of both social cognition and neurocognition, with more focus on the latter.

Social cognitive remediation therapy (SCRT) is an approach focusing mainly on social cognition in patients with schizophrenia (58, 63). As of today, two types of SCRTs are being...
developed: targeted and broad-based SCRTs. Targeted SCRTs address only the remediation of one specific social cognitive deficit (e.g., facial affect recognition) (64), whereas broad-based SCRTs address multiple social cognitive domains (65). Integrative broad-based SCRTs combine the improvement of social cognitive domains with other therapy techniques, such as Cognitive Behavioral Therapy (CBT) (66), cognitive remediation (67, 68) or social skills training (69–71). It is advisable to use an integrative approach involving both neurocognitive and social-cognitive domains, as these lead to greater generalization effects on functional outcome (53, 72, 73). In light of previous studies, we consider integrative broad-based SCRTs a promising treatment to reduce social cognitive impairments and enhance functioning in schizophrenia. Therefore, we decided to use this type of treatment approach for the current study.

METHODS

Aims and Hypotheses

This study’s main goal is to determine the effects of combined cTBS over rIPL and SCRT on gesture performance and social functioning in patients with schizophrenia. In addition, we aim to investigate neurocognitive, social cognitive, motor, clinical and neural effects of both interventions as secondary outcome measures. As cTBS enhances neuroplasticity and improves use of neural resources (46, 74), we expect administration of cTBS to facilitate SCRT training effects. Additionally, we hypothesize that the expected improvement of gesture performance will have positive effects on functional outcome, as both have been reported to be linked in schizophrenia (20). At the neural level, we hypothesize that the brain activity of patients will converge to the brain activity of healthy controls after both interventions, especially within the praxis network (39, 40).

This randomized controlled trial (RCT) will include three patient groups (see Figure 1). First, group A will receive real cTBS and real SCRT. Second, group B will receive sham cTBS and real SCRT. Third, group C will receive no cTBS and sham SCRT. In this study, we will also include a fourth group consisting of healthy controls, who will be assessed twice without any intervention in between. We expect the combination of cTBS and SCRT to show positive effects on both primary and secondary outcomes in patients with schizophrenia spectrum disorders. As such, we expect group A to have superior performance over group B and C in gesture performance and functional outcome after intervention (A > B > C).

Setting and Enrollment

Study Design

This will be a three-arm, double-blind, randomized, sham-controlled trial of add-on brain stimulation and SCRT to
with schizophrenia spectrum disorders. 

**Exclusion criteria**

- Substance abuse or dependence other than nicotine
- Past or current medical or neurological conditions associated with impaired or aberrant movement, such as brain tumors, stroke, Parkinson’s disease, Huntington disease, dystonia, or severe head trauma with subsequent loss of consciousness.
- Epilepsy or other convulsions
- History of any hearing problems or ringing in the ears
- Standard exclusion criteria for MRI scanning and TMS, e.g., metal implants, claustrophobia
- Women who are pregnant or breast feeding or intention to become pregnant
- Claustrophobia
- Substance abuse or dependence other than nicotine
- History of any psychiatric disorder or any first-degree relatives with schizophrenia spectrum disorders.
- Epilepsy or other convulsions
- Claustrophobia

improve nonverbal communication skills and overall functioning in schizophrenia spectrum disorders. This single-site trial will be conducted at the University Hospital of Psychiatry and Psychotherapy, Bern.

**Study Population**

Patients will be asked for participation at the outpatient departments of the University Hospital of Psychiatry and Psychotherapy, Bern and will be screened with the Structured Clinical Interview for DSM-5 (SCID). Healthy participants will be recruited by word-of-mouth and flyers in public places (e.g., grocery stores, pharmacies, gyms) in Bern. Participants will be eligible for study entry if they meet the criteria listed in Table 1.

**Interventions**

**Implementation of Real/Sham Continuous Theta Burst Stimulation**

Patients will receive ten cTBS sessions in total during the first 2 weeks of intervention. Each session (sham and real cTBS) will last 17 min consisting of two 44 s stimulations over rIPL separated by a 15-min break. For each stimulation of 44 s, we will apply 801 pulses at 50 Hz over the right IPL at an intensity of 100% of the resting motor threshold. Hence, the entire session will consist of 1,602 pulses. Sham cTBS will be delivered with a placebo-coil without any magnetic emission.

**Implementation of Real/Sham Social Cognitive Remediation Therapy**

Real/sham SCRT will be conducted bi-weekly for 8 weeks, totaling 16 sessions of 90 min. Each group will consist of six to eight patients led by a head-therapist (VC) and a co-therapist (FW). INT-expert (DM) will train both therapists and supervises the course of the sessions.

For this trial, we will tailor an SCRT based on the INT manual (58, 59). This SCRT will include the entire social cognitive part of the original INT (consisting of a minimum of 30 sessions) and two INT neurocognitive modules. As such, we will use psychoeducation and Cognitive Behavioral Therapy for Psychosis (CBTp) techniques. This intervention will have the main goal of improving gesture deficits in schizophrenia and will be separated in five blocks; each including neuro-

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**Table 1** | Eligibility.

**Inclusion criteria**

- Age between 18 and 65 years
- Right-handedness
- Patients only: diagnosis of schizophrenia spectrum disorders according to DSM-5

**Exclusion criteria**

- Substance abuse or dependence other than nicotine
- Past or current medical or neurological conditions associated with impaired or aberrant movement, such as brain tumors, stroke, Parkinson’s disease, Huntington disease, dystonia, or severe head trauma with subsequent loss of consciousness.
- Epilepsy or other convulsions
- History of any hearing problems or ringing in the ears
- Standard exclusion criteria for MRI scanning and TMS, e.g., metal implants, claustrophobia
- Women who are pregnant or breast feeding or intention to become pregnant
- Claustrophobia
- Substance abuse or dependence other than nicotine
- History of any psychiatric disorder or any first-degree relatives with schizophrenia spectrum disorders.
- Epilepsy or other convulsions
- Claustrophobia

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**Table 2** | SCRT therapy contents a trained cognitive processes.

| Block 1: Emotion perception and expression | Block 2: Verbal/visual learning and memory | Block 3: Social perception and theory of mind | Block 4: Working memory | Block 5: Social schema |
|--------------------------------------------|---------------------------------------------|---------------------------------------------|------------------------|----------------------|
| Introductory session: Psychoeducation topics | Training session: Compensatory and restitution exercises with interactive and computerized exercises | Transfer session: Practicing coping strategies in daily life with homework |
| Six basic emotions: their function, their expression (e.g., gestures) and their effect on perception/attention | Affect recognition and affect expression | Practicing newly learned affect recognition strategies with their regular environment |
| Short term memory, long term memory and prospective memory | Mnemonic strategies (e.g., chunking, external memory aids such as calendars and post-its) | Practicing familiar and newly learned mnemonic strategies |
| Key social stimuli and theory of mind | Observation of social encounters (e.g., with pictures, videos, and role play) and interpretation of social information | Practicing a more fact-oriented social perception (rather than assumptions-based) with their regular environment |
| Selective attention, working memory and how to reduce distractibility | Cognitive flexibility, selective attention, ability to inhibit cognitive interference (e.g., with computer tasks) | Practicing newly learned attention-focusing strategies |
| Norms and roles on social behavior and use of social knowledge | Social norms and behavioral sequences (e.g., with role play), recognition of own norm-deviating behavior and building strategies to change it if necessary, as well as coping with social stigma | Practicing newly learned social strategies in role play during group therapy and with their regular environment |
and social cognitive MATRICS-domains (see Table 2). The first, third and fifth block will focus predominantly on using and interpreting nonverbal cues in social contexts. The second and fourth blocks will address memory and attention, both of which are essential for functioning in social interaction. Three sessions will be dedicated to each block, totaling 15 sessions overall. With each session, the content of the blocks will increase in complexity. A final 16th session will be added, in which the content delivered in all previous five blocks will be summarized.

Each block will start with an introductory session, followed by a training session (i.e., compensation and restitution sessions), and a transfer session (see Table 2). During the introductory sessions, the MATRICS domains will be presented with a great focus on their everyday use and individual self-reference. The introductory sessions include psychoeducation on the respective neurocognitive and social domains. During the training sessions, we will determine patients’ strongest coping strategies, establish solution-oriented awareness, and train cognitive domains with various exercises (e.g., computerized cognitive tasks or role play exercises). The transfer sessions will work on the principle “rehearsal learning” (75, 76), meaning patients repeatedly apply the newly learned strategies in their daily life to restore social cognitive functions. The treatment goal will be to develop more coping strategies and enhance social skills to increase overall functioning. The therapists will follow a script for quality assurance and treatment fidelity.

Sham SCRT will consist of psychoeducation on sleep hygiene, exercise, stress, and music, as well as leisure activities, and mindfulness-based exercises (e.g., raisin meditation or walking meditation in a nearby park in Bern). Patients receiving this group therapy will also benefit from an interactive environment. The main difference with the real SCRT will be that sham SCRT will not include any (social) cognitive training, nor active transfer of skills into daily life.

### TABLE 3 | Time-points of assessments.

| TIME (week) | Screening | Baseline | Week 2 tests | Week 8 tests | Follow-up |
|-------------|-----------|----------|--------------|--------------|-----------|
| Eligibility screening | X | | | | |
| Informed consent | X | | | | |
| Allocation | X | | | | |
| Interventions | | | | | |
| Real and sham brain stimulation | | | | | |
| Real and sham group therapy | | | | | |
| Assessments | | | | | |
| Gesture tests | X | X | X | X | X |
| Clinical rating scales | X | X | X | X | X |
| Community functioning | | X | X | X | |
| Neuroimaging | X | X | | | |

### Primary and Secondary Outcomes

#### Behavioral and Clinical Assessments

The primary outcome of this study will be hand gesture performance, which will be assessed with the Test of Upper Limb Apraxia (TULIA) (77). TULIA includes 48 items in two domains: imitation (following demonstration) and pantomime (after verbal command). The test has three semantic categories of gestures: communicative (intransitive), object-related (transitive), or meaningless. Item ratings range from 0 to 5. If the participants make content errors (e.g., perseverations, substitutions), they will get 0–2 points per item. If the participants make spatial or temporal errors, they will get 3–4 points. Perfect performance equals 5 points, which is the maximum score per item. The highest TULIA total score is 240. A cutoff score will be used to measure gesture deficits in schizophrenia with < 210 TULIA total score (17). Gesture performance will be recorded on video and later evaluated by an independent examiner who is blinded to the groups or timing of the assessment. We will assess gesture performance using TULIA at four different time points (see Table 3).

Secondary outcomes will include additional nonverbal communication, cognitive, clinical, and functional assessments, as well as self-reports. Nonverbal communication will be tested with the Profile of Nonverbal Sensitivity (PONS) (78) assessing nonverbal social perception, and the modified postural knowledge task (79, 80) measuring gesture perception. Together, TULIA, PKT, and PONS assess nonverbal communication, as they include the production, the recognition, and the interpretation of gestures. History of symptoms and medication in patients will be assessed with The Comprehensive Assessment of Symptoms and History (CASH) (81). Self-reports, clinical scales, motor scales, cognitive tests and functional assessments are listed in Table 4.

Outcomes will be measured during four different time points: baseline, after tTBS (week 2), after SCRT (week 8) and follow-up (week 32) (see Table 3). At baseline, week 8 and week 32, the primary and all secondary outcomes will be tested. At week 2, the primary and a few secondary outcomes (i.e., nonverbal communication and clinical assessments) will be measured. Additionally, at baseline and week 8, neuroimaging data will be acquired to test the neural effects of the treatments.

#### Magnetic Resonance Imaging Measurements

Neuroimaging will include structural T1, arterial spin labeling (ASL), diffusion tensor imaging (DTI), blood oxygenation level dependent (BOLD) resting state and fMRI tasks. MRI acquisition will be performed at a 3T SIEMENS MAGNETOM Prisma at the Swiss Institute for Translational and Entrepreneurial Medicine (SITEM), Bern, Switzerland. We will use a 20-channel radio-frequency head coil (Siemens, Germany) for all acquisitions.

#### Functional Magnetic Resonance Imaging and Tasks

We will administer three different fMRI tasks to assess gesture planning/execution, perception, and interpretation (see Figure 2). First, gesture planning and performance will be assessed with an adapted version of the gesture task created by...
### TABLE 4 | Primary and secondary outcomes.

| Assessments                  | References |
|------------------------------|------------|
| **Self-reports**             |            |
| Brief Assessment of Gestures (BAG) (95) |            |
| Self-report of negative symptoms (SNS) (96) |            |
| The satisfaction with therapy and therapist scale-revised (STTS-R) for group psychotherapy (97) |            |
| **Psychopathology**          |            |
| Positive and negative syndrome scale (PANSS) (98) |            |
| Brief negative symptom scale (BNSS) (99) |            |
| Thought and language disorder (TALD) (100) |            |
| Frontal assessment battery (FAB) (101) |            |
| Bern psychopathology scale (BPS) (102) |            |
| **Motor scales**             |            |
| Neurological evaluation scale (NES) (103) |            |
| Bush Francis catatonia rating scale (BFCRS) (104) |            |
| Salpêtrière retardation rating scale (SRRS) (105) |            |
| Unified Parkinson’s disease rating scale (UPDRS) (106) |            |
| Abnormal involuntary movement scale (AIMS) (107) |            |
| **Behavioral tests**         |            |
| Postural knowledge test (PKT) (15, 26, 80) |            |
| Profile of nonverbal sensitivity (PONS) (78) |            |
| Coin rotation                | (108)      |
| Test of Upper Limb Apraxia (TULIA) (77) |            |
| **Neuro- and social cognition** |            |
| Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) (109) |            |
| Digit span backward (DSB) (110) |            |
| Test of nonverbal Intelligence (TONI) (111) |            |
| EMOREC-B (56)                | (56)       |
| Hinting task (HT)            | (112)      |
| EmBODY tool                  | (113)      |
| **Functional assessments**   |            |
| Global assessment of functioning (GAF) (88) |            |
| Social and occupational functioning assessment score (SOFAS) (114) |            |
| Personal and social performance (PSP) (114) |            |
| University of California, San Diego performance-based skills assessment brief (UPSA-b) (115) |            |
| Social level of functioning (SLOF) (116) |            |

Stegmayer et al. (39) and Kroliczak and Frey (82). In an event related design, participants will be presented with 30 gestures in a random order: 10 meaningless (e.g., “raise your thumb and your index finger”), 10 meaningful gestures (e.g., “wave goodbye”) and 10 control sentences with no gesture performance expected (e.g., “the weather is bad”). Second, we will use the Postural Knowledge Task (PKT) (15, 26, 80) to assess participants’ gesture perception. Participants will be presented with pictures of people performing gestures (20 trials), while the hands executing those gestures are missing. Participants will be asked to choose the correct hand gesture from three choices provided. In the control condition (20 pictures), participants will be asked to indicate if the person performing the gesture is either male or female. Third, we will use the point-light-display (PLD) method to assess dynamic gesture perception. Here, human biological movements will be depicted by 12 point-light dots on the main joints of a human actor in the absence of any other visual characteristics (83–85). For our task, 40 videos of one PLD agent will be shown to perform different communicative gestures while the other PLD agent imitated/followed these performed gestures (26, 86). Participants’ task will be to identify which PLD was imitating/following the other.

### Allocation and Randomization

Interventions will start in blocks as soon as 6–8 participants can be randomized to three groups: Group A, group B or group C (see Figure 1). Patients will not know which treatment they receive; they will be allocated to one of three treatment arms in a blinded manner.

### Statistical Considerations and Plan

Assuming a medium effect size ($f = 0.15$) in a repeated measures ANOVA with moderate-high correlation between time points (0.75), a power of 0.95 and an alpha = 0.05, we will need 72 patients (24 per group). In addition, a control group of 24 healthy subjects will be required. All four groups will be compared pre-to-post with an interval of 8 weeks (see Figure 1). The main effects of the combined interventions on the primary and secondary outcomes will be calculated in a repeated measures design including 3 main time points (Baseline, week 2, and week 8) and three patient groups (A, B, and C). With the latest SPSS and R versions, we also will run additional (partial) correlations, linear regressions, MANCOVAS using covariates (e.g., age, education, and medication).

### Trial Status

Study recruitment started on the 17th December 2019. The first group started with both interventions on the 24th February 2020. The study was impacted by the federal measures against the COVID-19 pandemic. As of June 2022, we recruited 65 patients and 36 healthy controls. We completed baseline assessments with 62 patients and 33 healthy
controls. We finished week-8 assessments with 36 patients and 32 controls.

**DISCUSSION**

**Relevance of the Current Study**

With this study, we will run one of the few prospective, sham-controlled RCTs addressing both gesture deficits and poor functioning in schizophrenia. Ameliorating functional outcome as a means of reintegrating patients into society has become one of the most central goals of psychiatric rehabilitation (87–89). Despite advances in antipsychotic medications and psychotherapies, functional recovery rates of schizophrenia patients have not increased substantially over the last 30 years (90, 91). Schizophrenia is not only a major burden for patients, but also a great economic strain for society, as patients with schizophrenia make heavy use of inpatient services and require...
financial support. It is urgent to develop psychiatric treatments that help patients to maintain interpersonal relationships and facilitate independent living. As gesture deficits in schizophrenia are highly correlated to overall functioning in daily life (20) and effective therapies reducing nonverbal communication deficits are lacking, it is clear that we need to establish interventions that tackle both (46, 92).

Advantages
The design of this RCT encompasses numerous advantages. The main strength of our study is the combination of two interventions; coupling brain stimulation with group therapy may exert cumulative therapeutic effects in gesturing and functioning in schizophrenia (20). Additionally, cTBS enhances neuroplasticity in schizophrenia patients (46, 74) and thus, may facilitate SCRT training effects. Thanks to the two comparators (sham cTBS and sham SCRT) we can evaluate the therapeutic effects of both interventions on behavioral, clinical, and neural levels. Also, we may find insights to predictors of treatment outcome. Further, the RCT design allows elimination of selection bias in treatment assignment and enables blinding from assessors and participants. Moreover, by collecting detailed demographic information over time, we will be able to correct for age, gender, education and antipsychotic medication dosage. Longitudinal data allows exploration of change in our patients, and thus, gives insight on the longevity of treatment effects. For example, our design may shed light on factors that are essential for the transfer of coping strategies. Most importantly, we are running one of the very few RCT on SCRT to involve acquisition of neuroimaging data before and after intervention. We can directly compare neural alterations to potential behavioral changes after the interventions. If this study proves to be successful it has the potential to be beneficial for other psychiatric disorders, which exhibit similar socio-cognitive dysfunctions such as depression (93, 94).

Limitations
This RCT entails a few limitations. First, we cannot eradicate the influence of medication; most patients suffering from schizophrenia are on antipsychotic treatment and other medication (e.g., blood pressure suppressants, antidepressants). However, for antipsychotic medication, we will control for Olanzapine equivalents in our statistical analyses. Second, we cannot eliminate gains linked to repeated test exposure as a result of retesting the same test under comparable conditions (i.e., retest effects). We counter these effects by randomizing the order of our test items for most of our assessments. Additionally, the time between most of our assessments makes training effects quite unlikely (i.e., 8 weeks, 32 weeks). Third, some of the data we collect are self-reports. Due to the subjective nature of self-reports, their psychometric aspects (e.g., reliability and validity) can be questionable or subject to biases (e.g., response bias). However, self-reports are necessary. For example, it is essential to compare patients’ subjective symptoms before and after intervention to find out if we are helping them. Fourth, another concern is the generalizability of the trial results. Participation in our study is only appropriate for a subgroup of schizophrenia patients, as it consists of 30 meetings in 3 months. As such, we can only include stable outpatients with good time management, commitment and tolerance to additional stress. This might cause the data collection to become arduous and dropout rates to be high.

CONCLUSION
In summary, this study explores the combination of cTBS and SCRT to improve gesture skills and social functioning in schizophrenia. This research project is of great importance as treatment options alleviating nonverbal communication deficits are clearly lacking. If this study proves to be successful, it has the potential to change the course of current treatment methods and greatly improve social functioning, as well as the quality of life of patients with schizophrenia.

ETHICS STATEMENT
The studies involving human participants were reviewed and approved by the Kantonale Ethikkommission Bern (KEK). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS
VC contributed to recruit participants, organizes the study procedures, conducts assessments, carries out both interventions, and drafted the manuscript. AP supervised the study procedures. DM trained the head therapist and co-therapists in SCRT and supervised the SCRT sessions. SW designed the study, obtained funding and ethics approval, wrote the study protocol, and registered the study at the clinical trials. All authors discussed and critically revised the manuscript.

FUNDING
This study was funded by the Swiss National Science Foundation (grant #184717 to SW).

ACKNOWLEDGMENTS
We thank Florian Weiss (FW) and Florence Ibrahim for being our SCRT co-therapists. We thank Karl Verfaillie for providing us with the PLD videos.
57. Moritz S, Klein JP, Lysaker PH, Mehl S. Metacognitive and cognitive-behavioral interventions for psychosis: multidimensional structure, clinical correlates, and relationship with functional outcome. Schizophr Res. (2011) 125:143–51. doi: 10.1016/j.schres.2010.11.007

58. Schmidt SJ, Mueller DR, Roder V. Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: empirical review and new results by structural equation modeling. Schizophr Bull. (2011) 37:541–54. doi: 10.1093/schbul/sbr079

59. Green MF, Nuechterlein KH. The MATRICS initiative: developing a consensus cognitive battery for clinical trials. Schizophr Res. (2004) 72:1–3. doi: 10.1016/j.schres.2004.09.006

60. Brown EC, Tas C, Brune M. Potential therapeutic avenues to tackle social cognition problems in schizophrenia. Expert Rev Neurother. (2012) 12:71–81. doi: 10.1586/ern.11.183

61. Mueller DR, Schmidt SJ, Roder V. One-year randomized controlled trial and follow-up of integrated neurocognitive therapy for schizophrenia outpatients. Schizophr Bull. (2015) 41:604–16. doi: 10.1093/schbul/sbu223

62. Moritz S, Klein JP, Lysaker PH, Mehl S. Metacognitive and cognitive-behavioral interventions for psychosis: new developments. Dialogues Clin Neurosci. (2019) 21:309–17. doi: 10.31867/DCNS.2019.21.3/moritz

63. Mueller DR, Roder V. Integrated psychological therapy for schizophrenia patients. Expert Rev Neurother. (2007) 7:1–3. doi: 10.1586/14737577.7.1.1

64. Roder V, Muller DR. INT – Integrierte Neurokognitive Therapie Bei Schizophrenen Erkrankten. Berlin: Springer (2013). doi: 10.1007/978-3-642-21440-0

65. Mueller DR, Khalezi Z, Benzing V, Castiglione CI, Roder V. Does integrated neurocognitive therapy (INT) reduce severe negative symptoms in schizophrenia outpatients? Schizophr Res. (2017) 188:92–7. doi: 10.1016/j.schres.2017.01.037

66. De Mare A, Cantarella M, Galeoto G. Effectiveness of integrated neurocognitive therapy on cognitive impairment and functional outcome for schizophrenia outpatients. Schizophr Res Treatment. (2018) 2018:2360697. doi: 10.1155/2018/2360697

67. Mueller DR, Khalezi Z, Roder V. Can cognitive remediation in groups prevent relapses? Results of a 1-year follow-up randomized controlled trial. J Neurol Ment Dis. (2020) 208:362–70. doi: 10.1097/NMD.0000000000001146

68. Wolwer W, Frommann N. Social-cognitive remediation in schizophrenia: generalization of effects of the training of affect recognition (TAR). Schizophr Bull. (2013) 37:563–70. doi: 10.1093/schbul/bst071

69. Wolwer W, Frommann N, Halmann S, Piaszek A, Streit M, Gaebel W. Remediation of impairments in facial affect recognition in schizophrenia: efficacy and specificity of a new training program. Schizophr Res. (2005) 80:295–303. doi: 10.1016/j.schres.2005.07.018

70. Grant N, Lawrence M, Preti A, Wykes T, Cella M. Social cognition interventions for people with schizophrenia: a systematic review focusing on methodological quality and intervention modality. Clin Psychol Rev. (2017) 56:35–64. doi: 10.1016/j.cpr.2017.01.001

71. Dark F, Harris M, Gore-Jones V, Newman E, Whiteford H. Implementing cognitive remediation and social cognitive interaction training into standard psychosis care. BMC Health Serv Res. (2018) 18:458. doi: 10.1186/s12913-018-3240-5

72. Wykes T, Van Der Gaag M. Is it time to develop a new cognitive therapy for psychosis–cognitive remediation therapy (CRT)? Clin Psychol Rev. (2001) 21:1227–56. doi: 10.1016/S0272-7358(01)00104-0

73. Cavallaro R, Anselmetti S, Poletti S, Bechi M, Ermoli E, Cocchi F, et al. Computer-aided neurocognitive remediation as an enhancing strategy for schizophrenia rehabilitation. Psychiatry Res. (2009) 169:191–6. doi: 10.1016/j.psychres.2008.06.027

74. Muller DR, Roder V, Brenner HD. Effectiveness of integrated psychological therapy (IPT) for schizophrenia patients: a meta-analysis. Schizophr Res. (2004) 67:202–202.

75. Roder V, Muller DR, Brenner HD. Integrated psychological therapy (IPT) for schizophrenia patients in different settings, patient sub samples and site conditions: a meta-analysis. Eur Psychiatry. (2004) 19:76s–7s.

76. Kopelowicz A, Liberman RP, Zarate R. Recent advances in social skills training for schizophrenia. Schizophr Bull. (2006) 32 Suppl 1:S12–23. doi: 10.1093/schbul/sbl023

77. McGurk SR, Twamley EW, Sitzer DL, Mchugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry. (2007) 164:1791–802. doi: 10.1176/appi.ajp.2007.07060906

78. Eack SM, Pogue-Geile MF, Greenwald DP, Hogarty SS, Keshavan MS. Mechanisms of functional improvement in a 2-year trial of cognitive enhancement therapy for early schizophrenia. Psychol Med. (2011) 41:1253–61. doi: 10.1017/S0033291710001765

79. Goldsworthy MR, Valence AM, Yang R, Pitcher JB, Ridding MC. Combined transcortical alternating current stimulation and continuous theta burst stimulation: a novel approach for neuroplasticity induction. Eur J Neuropsychopharmacol. (2016) 23:472–7. doi: 10.1177/1078101714563246

80. Kolb AB, Yett C, Druga D. Learning styles and learning spaces: enhancing experiential learning in higher education. Acad Manage Learn Educ. (2005) 4:193–212. doi: 10.5465/amle.2005.17268566

81. Beidas RS, Cross W, Dorsey S. Show me, don’t tell me: behavioral rehearsal as a training and analogue fidelity tool. Cogn Behav Pract. (2014) 21:1–11. doi: 10.1017/cbp.2013.04.002

82. Vanbellingen T, Kersten B, Van Hemelrijk B, Van De Winckel A, Bertschi L, Muri R, et al. Comprehensive assessment of gesture production: a new test of upper limb apraxia (TULIA). Clin Neuropsychol. (2010) 17:59–66. doi: 10.1177/1473744710371843

83. Rosenthal R, Hall JA, Di Matteo MR, Rogers PL, Archer D. Sensitivity to Nonverbal Communication: The PONS Test. Baltimore, MD: John Hopkins University Press.

84. Mozar M, Roth LJJG, Anderson JM, Crucian GP, Heilman KM. Postural knowledge of transitive pantomimes and intransitive gestures. J Int Neuropsychol Soc. (2002) 8:958–62. doi: 10.1017/S1355617702870114

85. Bohlhalter S, Vanbellingen T, Bertschi M, Wurtz P, Cazzoli D, Nyffeler T, et al. Interference with gesture production by theta burst stimulation over left inferior frontal cortex. Clin Neurophysiol. (2011) 122:1197–202. doi: 10.1016/j.clinph.2010.11.008

86. Andreasen NC, Flaum M, Arndt S. The comprehensive assessment of symptoms and history (Cash) – an instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry. (1992) 49:615–23. doi: 10.1001/archpsyc.1992.0182008023004

87. Krolczak G, Frey SH. A common network in the left cerebral hemisphere represents planning of tool use pantomimes and familiar intransitive gestures at the hand-independent level. Cerebral Cortex. (2009) 19:2396–410. doi: 10.1093/cercor/bhn261

88. Johansson G. Visual perception of biological motion and a model for its analysis. Percept Psychophys. (1973) 14:201–11. doi: 10.3758/BF03222738

89. Pavlidou A, Schnitzler A, Lange J. Interactions between visual and motor areas during the recognition of plausible actions as revealed by...
