Boost rTMS for AVH

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Therapeutic Response and Neurobiological Prediction Markers in Auditory Verbal Hallucinations

Protocol Number: 1

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the BioMEND Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Boost rTMS for AVH – Therapeutic Response and Neurobiological Prediction Markers in Auditory Verbal Hallucinations
Study Description:	This is a randomized, placebo controlled, double-blind clinical trial. We aim to examine the efficacy of repeated transcranial magnetic stimulation (rTMS) for the treatment of auditory verbal hallucinations (AVH) in patients with schizophrenia who are not taking antipsychotic medication. We employ a novel, accelerated protocol with only 4 sessions of low-frequency rTMS in one day. The effects of this accelerated protocol will be compared to the sham stimulation. Additionally, we will examine the effects of rTMS on a neurophysiological level by evaluation mechanism of action in the temporo-parietal lobe.
Objectives:	Primary Objective: Examine the efficacy of low-frequency rTMS for AVH in patients with a schizophrenia spectrum disorder. Secondary Objectives: Examine the effects of rTMS on the quality of AVH, positive symptoms, general psychopathology, and the global level of functioning of these patients. Last, confirm that rTMS has no side effects on cognitive functioning. Determine the neuroimaging-related biomarkers associated with response to rTMS using the baseline imaging parameters (rCBF, resting fMRI, T1, and DTI) to predict response to rTMS treatment. Further,

compare pre- and post-treatment imaging parameters (rCBF, resting fMRI, T1, and DTI) to characterize rTMS effects on AVH.

Endpoints:

Primary Endpoint:

- AVH assessed using the Hallucination Change Scale (HCS) at baseline (first visit), after the last TMS session, after the post-MRI.

Secondary Endpoints:

a) Assessment of the qualitative content of hallucinations will be assessed using the revised Beliefs About Voices Questionnaire (BAVQ-R)
b) Assessment of AVH as part of positive symptoms will be assessed with the Brief Psychiatric Rating Scale (BPRS)-subscale that includes "Hallucinatory Behavior", "Conceptual Disorganization", "Suspiciousness", and "Unusual Thought Content".
c) Global functioning will be assessed using the Clinical Global Impression (CGI) and General Assessment of Functioning (GAF) questionnaires.
d) Cognitive functioning will be assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (rBANS).

Neurophysiological changes using magnetic resonance imaging (MRI) are investigated as predictors for rTMS treatment response.

Study Population:

N = 40

- Male and female subjects 18 to 65 years of age
- DSM V diagnosis of schizophrenia (295.90), schizoaffective disorder (295.70) or brief psychotic disorder (298.80) confirmed by SCID-V interview currently experiencing AVH in the acute phases of the disorder as assessed with the revised Beliefs About Voices Questionnaire (BAVQ-R).
- Patient agrees to rTMS for AVH treatment for 1 day before standard medication therapy.
- Right-handedness assessed with the Edinburgh Handedness Inventory
- Patient is competent to provide informed consent
- Inpatient at the Zucker Hillside Hospital
- No history of seizures

Phase:

N/A

Description of Sites/Facilities Enrolling Participants:

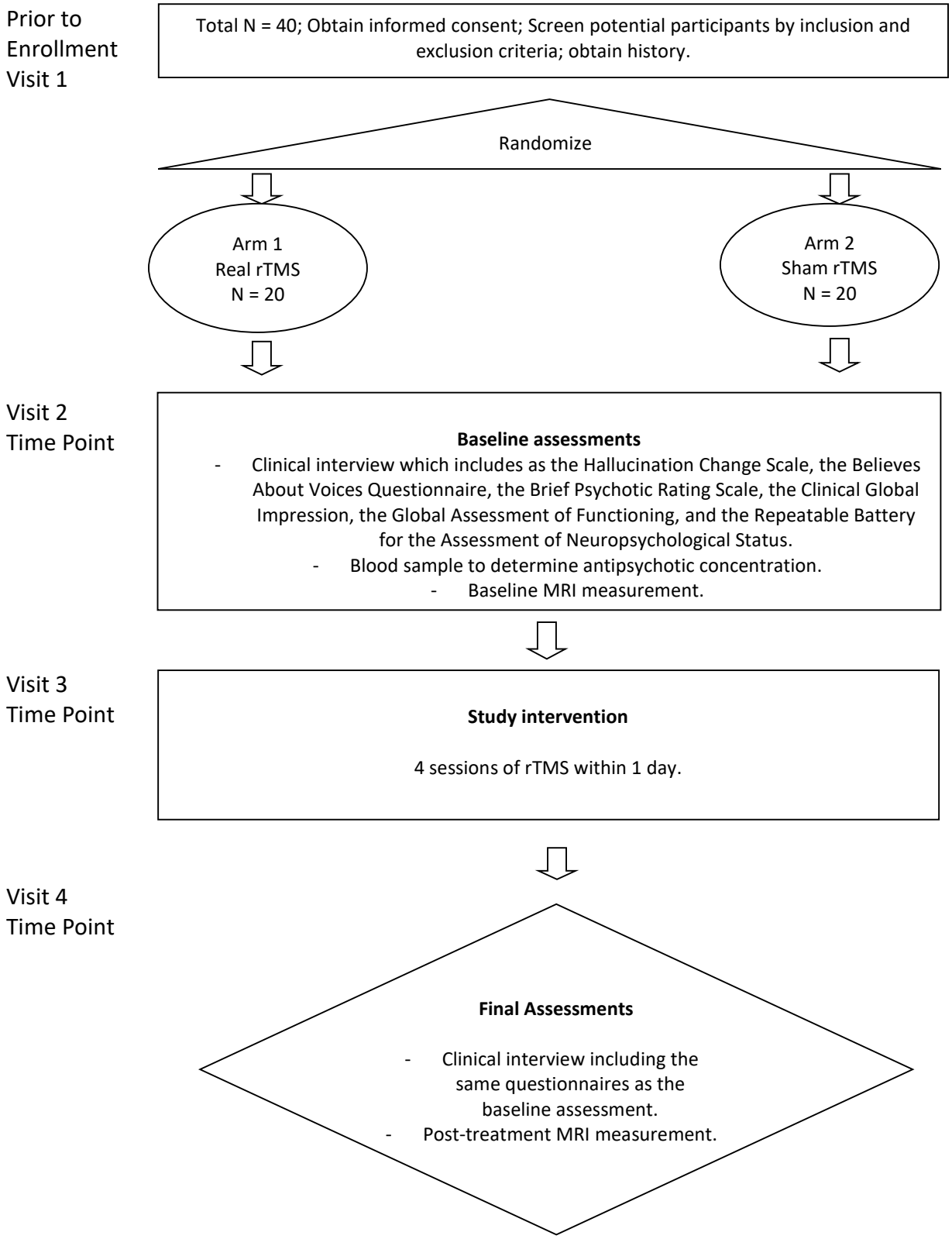
Participants will be recruited through the Zucker Hillside Hospital in-patient clinic. Recruitment will only take place at this side and no sides outside of the United States are included.

Description of Study Intervention:

All patients receive 1Hz of rTMS over the Sylvian parietal temporal area (area Spt) four times on 1 day (1 pulse/second and a total of 1'000 pulses: 16 minutes' protocol at 100% of motor threshold modified based on

	Hoffman et al. (1999)). Area Spt will be localized via baseline structural imaging and our Localite TMS navigation system. Subjects will be withdrawn from the study if side effects become limiting, or if either the patient or principal investigator determine that rTMS should be discontinued.
Study Duration:	18 months in total including 12 months for recruitment and measurements plus 6 months for data analysis.
Participant Duration:	Each participant is enrolled for up to 4 days of measurements (minimum of 3 days).

1.2 SCHEMA


Prior to Enrollment Visit 1
Total N = 40; Obtain informed consent; Screen potential participants by inclusion and exclusion criteria; obtain history.
Randomize
Arm 1
Real rTMS
N = 20
Arm 2
Sham rTMS
N = 20
Visit 2 Time Point
Baseline assessments
- Clinical interview which includes as the Hallucination Change Scale, the Believes About Voices Questionnaire, the Brief Psychotic Rating Scale, the Clinical Global Impression, the Global Assessment of Functioning, and the Repeatable Battery for the Assessment of Neuropsychological Status.
- Blood sample to determine antipsychotic concentration.
- Baseline MRI measurement.
Visit 3 Time Point
Study intervention
4 sessions of rTMS within 1 day.
Visit 4 Time Point
Final Assessments
- Clinical interview including the same questionnaires as the baseline assessment.
- Post-treatment MRI measurement.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Visit Procedures	Screening	Enrollment/Baseline Assessment	Treatment Day	Follow-up Assessment
Informed consent	X			
Demographics	X			
Medical history	X			
Blood sample	X			
Randomization	X			
TMS screening questionnaire	X			
Administer study intervention			X	
Adverse event review and evaluation	X	X	X	X
Imaging assessment	X	X		X
Complete Case Report Forms (CRFs)	X	X	X	X

Note that the Screening Day is not specifically set. This day can either be on the first day of the study such that patients who are willing to participate could start immediately with the baseline measurements. While patients who are for example recruited in the evening would have their first day of the study on the following day. In the special case of enrollment on a Friday, the start of the study would be the following Monday. Thus, patients would have to declare that they do not want to take antipsychotics during the weekend and the time of the study. See section 2.3.1 “Known Potential Risks” for information.

Only for eligible patients for which an extra vial of blood was not collected for the measurement of serum level of antipsychotic, phlebotomy will be performed especially for this study in order to obtain the blood sample necessary to assess the serum antipsychotic concentration prior to the scanner.

2 INTRODUCTION

2.1 STUDY RATIONALE

Schizophrenia is a disorder that affects communication, cognition, and emotion and thus leads to a high degree of suffering for patients (Sukhwinder S Shergill, Murray, & McGuire, 1998) and even to suicide attempts (Hor & Taylor, 2010). Up to 70% of schizophrenia patients suffer from auditory verbal hallucinations (AVH) (Waters, 2012), one of the cardinal symptoms of schizophrenia.

The most conventional therapeutic strategy is antipsychotic medication. Yet, in about 20-30% of patients even extended antipsychotic medication does not ameliorate AVH (Sukhwinder S Shergill et al.,

2007) and is often accompanied by side effects (Leucht et al., 2009). Therefore, it is crucial to develop and assess promising, potentially beneficial therapeutic options.

Non-invasive brain stimulation techniques like repetitive transcranial magnetic stimulation (rTMS) have been proposed to disrupt mechanisms in question. In particular, low-frequency (LF) rTMS is thought to decrease cortical excitability. In schizophrenia, Hoffman et al. (1999) were the first to introduce rTMS for the treatment of refractory AVH. The authors used LF rTMS (1Hz) over the left temporo-parietal junction (TPJ) and showed a significant reduction in AVH severity with effects lasting up to 15 weeks. Following this promising result, several studies replicated these findings (Brunelin et al., 2006; Chibbaro et al., 2005; Hoffman et al., 2000; Hoffman et al., 2005; Hoffman et al., 2007; Jandl et al., 2006; Klirova et al., 2013; Lee et al., 2005; Poulet et al., 2005; Vercammen et al., 2009), but others did not (Blumberger et al., 2012; de Jesus et al., 2011; Fitzgerald et al., 2005; Hoffman et al., 2013; Lee et al., 2005; Loo, Sainsbury, Mitchell, Hadzi-Pavlovic, & Sachdev, 2010; McIntosh et al., 2004; Rosa et al., 2007; Saba et al., 2006; Schönfeldt-Lecuona et al., 2004; C. Slotema, Aleman, Daskalakis, & Sommer, 2012; C. W. Slotema et al., 2011).

This heterogeneity of results may be due to influencing factors such as rTMS protocols, parameters, and target regions. Nevertheless, a number of meta-analyses (Aleman, Sommer, & Kahn, 2007; Demeulemeester et al., 2012; Freitas, Fregni, & Pascual-Leone, 2009; C. W. Slotema, Blom, van Lutterveld, Hoek, & Sommer, 2014; C. W. Slotema, Dirk Blom, Hoek, & Sommer, 2010; Tranulis, Sepehry, Galinowski, & Stip, 2008) found significant effect sizes ranging from 0.42 to 1.04 for LF rTMS over the left TPJ. This indicates a medium to large effect for the treatment of AVH with rTMS. However, all studies so far investigated the effects of rTMS in treatment resistant schizophrenia patients as an ad-on or second-line treatment.

However, there are no studies to date that explored the effects of rTMS either as a first-line treatment or in the initial stage of the illness. This is surprising, considering the fact that rTMS is a safe treatment with minimal side-effects (Rossi, Hallett, Rossini, & Pascual-Leone, 2009) that could be used already in the earlier phase of treatment. Furthermore, another advantage of rTMS are the minimal side-effects associated with this treatment (Rossi et al., 2009). This stands in considerable contrast to the range of side-effects associated with antipsychotics (Leucht et al., 2017) that can be disabling leading to suffering for patients and lower quality of life. Therefore, it is crucial to develop new treatment options that in the future might provide alternatives to conventional therapy.

Noteworthy, previous studies in medicated patients focused mainly on treatment-resistant patients, which might be a special subgroup and not necessarily reflect the whole spectrum of schizophrenia patients including first episode patients who never had antipsychotic treatment. Therefore, investigating rTMS effects in patients from the whole schizophrenia spectrum are needed.

Further, the majority of studies used the standard protocol as described above that lasts for 10 consecutive days with one TMS session per day. Yet, daily administration of rTMS over the course of several days without antipsychotic medication could comprise risks, especially for patients suffering from additional psychotic symptoms. This may be one of the reasons that no study to date has investigated rTMS in patients with schizophrenia that did not take any antipsychotic medication.

Taken together, the crucial next step is (1) to explore the effects of rTMS in medication-free patients from the whole schizophrenia spectrum and (2) to use an accelerated protocol of multiple rTMS-sessions within a short period of time. To make this assessment feasible, considering that patients have to be off medication, the safest and also most efficient way is an accelerated rTMS protocol. The great advantage of such an approach is that the effects of rTMS can be investigated independently of potentially influencing effects of antipsychotics and at the same time assess the efficacy of rTMS within a very short amount of time.

In the proposed study, we aim to investigate the efficacy of rTMS as a potential treatment for AVH in schizophrenia besides an improved understanding of the neurobiology of schizophrenia and AVH and thus reduce suffering in patients and their relatives.

We will conduct a clinical trial in which we will collect neuroimaging data in patients undergoing one day of 4 sessions of LF rTMS. Imaging and neuropsychological data will be collected at baseline and at the end of the course of the treatment.

Background

Neuroimaging results in relation to AVH

Schizophrenia is a chronic psychiatric disorder associated with considerable morbidity and mortality (Dean, 2012). With a prevalence rate of 0.3 – 0.7 % of the population (van Os & Kapur, 2009), about 50 million people worldwide suffer from schizophrenia. Among these, up to 80% suffer from AVH (Linscott & Van Os, 2013), one of the most common symptoms of this disorder with diagnostic value. Due to their intrusive and often uncontrollable nature, AVH can be extremely emotionally distressing for patients and can lead to patients endangering themselves and others. Thus, an efficient therapeutic regimen is indispensable to lower suffering and costs. Unfortunately, therapeutic options are rather limited.

The most conventional therapeutic strategy is the use of antipsychotic medication, however, their efficacy is poor for many patients (Dean, 2012). In about 20 - 30 % even extended antipsychotic medication does not ameliorate AVH (Sukhwinder S Shergill et al., 1998). Also, many patients refuse medication or a necessary increase of the dosage even after exacerbation of symptoms. This may be due to the common side effects such as weight gain, somnolence, hyperprolactinemia, dystonia, and other movement disorders that, in some patients, require the dose or type of drug to be altered.

Beside conventional medicinal therapy, medication-free therapeutic regimens such as psychotherapy, psychoeducation, and psychosocial interventions offer some improvement with electroconvulsive treatment as a last resort. As a novel approach, non-invasive brain stimulation techniques such as transcranial magnetic stimulation (Hoffman et al., 1999; Hoffman et al., 2005; P Homan, Kindler, Hauf, Hubl, & Dierks, 2012; Philipp Homan et al., 2013; Jochen Kindler et al., 2013; J. Kindler et al., 2013; Kindler et al., 2012; C. W. Slotema et al., 2011) are being studied as options in the treatment of AVH with some promising findings.

Understanding the neuronal mechanisms underlying AVH, therefore, is of considerable scientific importance. First, structural alterations were found to be related to the severity of AVH: decreased gray matter (GM) volume in the left (Modinos et al., 2013) and right superior temporal gyrus (STG) and the left insula (Palaniyappan, Balain, Radua, & Liddle, 2012), decreased white matter (WM) integrity of the left arcuate fasciculus (Abdul-Rahman et al., 2012; Catani et al., 2011; De Weijer et al., 2011; Geoffroy et al., 2014; Daniela Hubl et al., 2004; McCarthy-Jones, Oestreich, Whitford, & Bank, 2015), as well as increased WM integrity in the arcuate fasciculus, the cingulum (Sukhwinder S Shergill et al., 2007), and the corpus callosum (D. Hubl et al., 2004; Mulert et al., 2012). Second, functional findings, e.g. summarized in the meta-analysis by Jardri et al.(2011), show a relationship between increased brain activity in fronto-temporal regions in the left hemisphere and in the hippocampal/parahippocampal gyrus and severity of AVH.

These results of structural and functional anomalies suggest that AVH arise from altered communication between brain regions and are not a result of localized alterations of single brain regions. This is in line with the idea of a fronto-temporal disconnection underlying AVH (Friston, 1998; Friston & Frith, 1995).

Brain stimulation using rTMS

Repetitive TMS uses a fluctuating magnetic field to induce a brief electrical current that generates an action potential propagating along neurons (Valero-Cabré, Payne, & Pascual-Leone, 2007; Valero-Cabré,

Payne, Rushmore, Lomber, & Pascual-Leone, 2005; Wagner, Valero-Cabre, & Pascual-Leone, 2007). In most studies, rTMS is applied over the course of several days causing short-term modulations of the target region and its connected network (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Valero-Cabré, Pascual-Leone, & Coubard, 2011). Low-frequency (LF) rTMS (1 pulse/second, 1 Hz) is thought to inhibit cortical excitability in the stimulated area. This effect depends not only on the stimulation frequency, but also on the time between pulses and other influencing factors (Lefaucheur et al., 2014).

In schizophrenia, Hoffman et al. (1999) were the first to introduce rTMS for the treatment of refractory AVH in treatment-resistant patients. The authors used LF rTMS over the left temporo-parietal junction (TPJ) and showed significantly reduced AVH severity with effects lasting up to 15 weeks. The TPJ is a sensory-motor integration area and is involved in the perception of speech (Benson et al., 2001; Fiez, Raichle, Balota, Tallal, & Petersen, 1996). The increased activity found in this region during AVH (S. S. Shergill, Bullmore, Simmons, Murray, & McGuire, 2000; Silbersweig et al., 1995) may arise from deficits in self-monitoring that, subsequently, lead to misinterpretation of inner speech (Frith, Friston, Liddle, & Frackowiak, 1992; Waters, 2012).

Since the first promising rTMS trials of Hoffman et al. (1999), many studies have used the classical LF stimulation pattern delivered to the left TPJ. Regarding this, meta-analyses (Aleman et al., 2007; Demeulemeester et al., 2012; Freitas et al., 2009; C. W. Slotema et al., 2014; C. W. Slotema et al., 2010; Tranulis et al., 2008) found significant effect sizes ranging from 0.42 to 1.04 which indicate a medium to large therapeutic effect of rTMS for the treatment of AVH.

However, most of the studies included patients with medication-resistant AVH. No study to date investigated rTMS in medication-naïve, high-risk individuals for psychosis or patients who are currently not taking antipsychotics who suffer from AVH in the relative absence of other severe positive or negative symptoms (C. W. Slotema et al., 2014). This is surprising, considering the fact that rTMS is a safe treatment with minimal side-effects (Rossi et al., 2009) that could be used already in the earlier phase of treatment. TMS could be applied as a first-line treatment for patients who primarily suffer from AVH, thus, exhaust other therapeutic options before turning to antipsychotics that are often associated with considerable side effects (Leucht et al., 2017) that impact on the patient's quality of life.

Furthermore, it is crucial to investigate the effects of brain stimulation independently of potentially influencing effects of antipsychotic medication. Teasing apart the effects of brain stimulation and antipsychotic drugs would allow a clearer assessment of the effects of brain stimulation and would help determine if brain stimulation techniques are useful as a first-line treatment or better implemented as an add-on to the conventional drug therapy. Yet, daily administration of rTMS over the course of several days without antipsychotic medication could comprise risks especially for patients suffering from further psychotic symptoms. Therefore, reducing the time of rTMS administration would, on the one hand, diminishes this risk and, on the other hand, reveals potentially beneficial effects of rTMS on AVH within a day, rather than two or more weeks typically needed with the classical rTMS protocol. Yet, no study to date has investigated rTMS for AVH in patients with schizophrenia who do not take antipsychotic medication. We aim to bridge this gap.

Following the above described line of thoughts, Holtzheimer et al. (2010) used an accelerated rTMS protocol of 15 sessions within 2 days in patients with treatment-resistant depression. Patients were stimulated with high-frequency rTMS in 5 sessions on the first day and 10 sessions on the second day. Being the first to use such an accelerated protocol in depression, Holtzheimer et al. (2010) showed promising results concerning safety and efficacy. This motivated further open-label studies investigating rTMS in depression, which found similarly promising results (McGirr, Van den Eynde, Tovar-Perdomo, Fleck, & Berlim, 2015; Tor, Gálvez, Goldstein, George, & Loo, 2016).

For AVH in schizophrenia, an accelerated protocol was used by Montagne-Larmurier et al. (2009) who administered two sessions of *high-frequency* rTMS (20Hz) on two days. Stimulation site was the posterior part of the left superior temporal sulcus that corresponds to the target area Spt proposed in this

study. The results were remarkable: Severity of AVH was significantly reduced ($p < .01$) with an effect size of 1.26 after the two day TMS treatment, lasting for 5.9 days (SD = 6.75). Notably, rTMS was well tolerated in all patients (no seizures) with headache as a side effect in only two cases. This study showing promising results of the accelerated protocol regarding safety and efficacy provides further evidence of the feasibility to shorten and thus accelerate rTMS protocols without loss of efficacy.

Yet, the majority of brain stimulation studies in schizophrenia-related AVH used *low-frequency* rTMS, but no study to date investigated the efficacy and safety of an accelerated low-frequency protocol. Low-frequency rTMS has the advantage of lower risk of side effects such as seizures than high-frequency rTMS (Rossi et al., 2009). Based on this and considering that in depression even 5 up to 10 sessions of high-frequency rTMS were applied, we expect that the application of 4 sessions of low-frequency rTMS will not impact on tolerability, safety or increased side-effects.

Based on this, we aim to assess the safety and efficacy of open-label accelerated rTMS, delivered over one day with four sessions, in first-episode schizophrenia patients who suffer from AVH and who decline first-line treatment with antipsychotic medication. We aim to further investigate the predictive value of cerebral blood flow, following the promising results of Homan et al. (2012), in first-episode schizophrenia patients.

In this project, we propose a translational approach to take the basic knowledge about the neurobiological underpinnings of AVH into direct clinical use, in a study of therapeutic outcome and related neurobiological changes and predictors of AVH.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

AVH symptomatology

Immediate risk

- Auditory verbal hallucinations can have different qualities such as being commenting, commanding, and/or threatening (e.g. harming oneself and others). These qualities can change over time and are thought to be related to factors such as stress (Upthegrove et al., 2016). AVHs during a phase of florid psychosis can have a more threatening character which in turn can lead to more stress and more psychotic symptoms. Therefore, a close monitoring of the patients´ hallucinations, well-being, and the content of the AVH is important. All study personnel are trained to detect signs of stress in patients and worsening of psychotic symptoms. Additionally, the Believes About Voices Questionnaire (BAVQ-R) will be given to patients at every visit to assess the content, severity, and distress associated with AVH. Patients will be asked to report about their AVH´s content and will be encouraged by the study coordinator to talk about changes in their mood and AVH content.
- In case a patient shows worsening of psychotic symptoms or, in the worst case, gets suicidal or homicidal within the three days of the study, participation is terminated and appropriate actions are initiated in accordance with the ward such as the application of antipsychotic medication given by the patient's treating clinician as per standard treatment guidelines and based on their best judgment. For this reason, the study staff will be in constant contact with the unit staff and the treating physician of the patient to work together with the best clinical interest for the patients' health.

Long-range risks

- There are no know long-range risks

Blood sample

Immediate risks

- We will obtain a blood sample to assess the serum concentration of the antipsychotic at the moment of hospitalization by adding an extra tube to the 2 that are routinely obtained via simple venipuncture as part of routine care in the emergency room. No phlebotomy will be performed at this point with a research indication if there is no clinical indication as per routine care. The additional blood sample will be collected in a third tube (approximately 2-3 mLs) from the same venipuncture for all patients that are hospitalized and potentially eligible to participate in the study. Therefore, the additional tube that is needed for the study does not constitute an additional risk.

Long-range risks

- There are no known long-range risks.

MRI

Immediate risks

- The risks of fMRI scanning are minimal. There is no ionizing radiation involved in MRI, and there have been no documented significant side effects of the magnetic fields and radio waves used on the human body to date.
- People have been harmed in MRI machines when they did not remove metal objects from their clothes or when others left metal objects in the room. All necessary precautions will be taken to prevent inadvertent presence of metal objects in the MRI room.
- Some subjects, even those without known history of claustrophobia may experience discomfort or even panic attacks in the enclosed setting of the magnet. All efforts will be taken to first calm subjects down and next to decide together with the participant whether or not to continue study participation. All subjects are informed that they can discontinue the procedure at any time, and receive instructions before scanning about communicating with the scanning system operators, which can be done either by a squeeze bulb kept in the subject's hand, or by voice through a microphone mounted inside the bore of the magnet, if they feel uncomfortable. Although, these scans are being done for research purposes, the images from the MRI will be reviewed by a physician who normally reads such images (such as a neuroradiologist). As a result, the subject will be informed of any unexpected findings. If our research yields any information that can be relevant in the subject's clinical management, we will notify them.

The occurrence of the MRI procedure and the subject's study participation may be documented in their medical record.

Long-range risks

- However, because the effects of strong magnetic fields on a fetus are not well documented at this time, pregnant women will be excluded from the study. Pregnancy is assessed with a pregnancy test prior to the two MRI measurements. People have been harmed in MRI machines when they did not remove metal objects from their clothes or when others left metal objects in the room.
- All necessary precautions will be taken to prevent inadvertent presence of metal objects in the MRI room. Some subjects, even those without known history of claustrophobia may experience discomfort or even panic attacks in the enclosed setting of the magnet. All efforts will be taken to first calm subjects down and next to decide together with the participant whether or not to continue study participation. An additional discomfort can be caused by the loud noise generated

by the rapidly changing magnetic field. It is standard to use earplugs or protective headphones to avoid discomfort and sensorineural hearing loss.

rTMS

Immediate risks

- TMS is a non-invasive treatment that is generally safe and well-tolerated. If local scalp pain or face muscle pain occurs, adjustment of the coil usually alleviates the pain. The most significant safety concern is seizure; however, as can be seen from Table 3, 1Hz rTMS for 1800 seconds is considered safe(Rossi et al., 2009). As a safety precaution, however, we will exclude patients with seizure disorders from this study. There are no additional significant risks due to study procedures.

Long-range risks

- The most common side effect is headache or pain, which is transient and responds well to combination of acetaminophen and ibuprofen (we will administer if patients require so). There are no known mechanisms through which the induced magnetic field produced during TMS stimulation could generate biological adverse effects in the absence of extraneous implanted metal in the skull or brain. That is the reason we will exclude all patients with metal implants (they would not be eligible because of the MRI component either).

Maximum established safe train of durations with rTMS

	Intensity (% of MT)				
Frequency	90%	100%	110%	120%	130%
1 Hz	> 1800.00 s	> 1800.00s	< 1800.00 s	> 360.00 s	> 50.00 s
5 Hz	> 10.00 s	> 10.00 s	> 10.00 s	> 10.00 s	> 10.00 s
10 Hz	> 5.00 s	> 5.00 s	> 5.00 s	4.20 s	2.90 s
20 Hz	2.05 s	2.05 s	1.60 s	1.00 s	0.55 s
25 Hz	1.28 s	1.28 s	0.84 s	0.40 s	0.24 s

Note.: s, seconds; MT, motor threshold; '>', maximum tested durations.

2.2.2 Known Potential Benefits

MRI

Immediate potential benefits

- There is no immediate potential benefit.

Long-range potential benefits

- Screening the brain with an MR allows us to investigate potential changes due to the rTMS treatment. Detecting these often subtle changes provides an objective measure of the effects of the treatment on the brain´s structural and functional properties. To evaluate the outcome of the treatment, MRI data is an essential tool.
  Also, the screening of the brain has the potential benefit of detecting abnormalities that might have otherwise been missed.

rTMS and AVH symptomatology

Immediate potential benefits

- The known immediate potential benefits include reduced severity of auditory verbal hallucinations immediately after the treatment.

Long-range potential benefits

- In schizophrenia, Hoffman et al.(1999) were the first to introduce rTMS for the treatment of refractory AVH in treatment-resistant patients. The authors used LF rTMS over the left temporo-parietal junction (TPJ) and showed significantly reduced AVH severity with effects lasting up to 15 weeks. Following this promising result, several studies replicated these findings (Brunelin et al., 2006; Chibbaro et al., 2005; Hoffman et al., 2000; Hoffman et al., 2005; Hoffman et al., 2007; Jandl et al., 2006; Klirova et al., 2013; Lee et al., 2005; Poulet et al., 2005; Vercammen et al., 2009).

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

MRI

The MRI measurement on the one hand constitutes of a minimal risk. On the other hand, analyzing the MR data does not only allow assessing the effects of rTMS on an objective, physiological level, but allows the clinical assessment of the brain physiology regarding preexisting anomalies and potential treatment-related changes. It is therefore crucial as a diagnostic and outcome measure.

rTMS & AVH symptomatology

Up to 70% of schizophrenia patients suffer from auditory verbal hallucinations (AVH), one of the cardinal symptoms of schizophrenia. Yet, in about 20-30% of patients even extended antipsychotic medication does not ameliorate AVH (Waters, 2012) and is often accompanied by side effects. Thus, new therapeutic options are needed. Studies using low-frequency rTMS over the left temporo-parietal junction have shown medium to large effect sizes. These results indicate that rTMS might be a promising option in the treatment of AVH. Therefore, it is vital to explore the effects of rTMS in medication-free individuals in the initial phase of psychosis and, secondly, to use an accelerated protocol of multiple rTMS-sessions within a short period of time. The reduced time of rTMS administration would diminish potential risks related to other psychotic symptoms and reveal rTMS effects on AVH within a few days. The considerable potential benefit for participating patients, especially for those in the treatment arm, overweighs the potential minimal side effects of a headache or itching pane at the side of stimulation. Further, the likelihood of seizures is very small, considering a low-frequency stimulation intensity.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Examine the efficacy of low-frequency rTMS for the treatment of AVH in patients with a schizophrenia spectrum disorder.	Our primary outcome will be the score of the Hallucination Change Scale (HCS) (Hoffman et al., 2003). Response criteria: a) Clinically significant improvement in AVH is	The HCS is used as our primary outcome measure. The scale will be anchored at baseline using the narrative description of AVHs provided by the patient for the prior 24 hours, which will be assigned a score of 10. For subsequent assessments, the HCS ranges from 0-20 (with a score of 20

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	defined as a score of <8 on the HCS (Hoffman et al., 2013) b) Drop-outs: defined as patients who discontinue treatment before completing the 4 rTMS sessions.	corresponding to hallucinations twice as severe as baseline) (Hoffman et al., 2003; Hoffman et al., 2013). The HCS is a frequently used assessment for AVH in schizophrenia (Hoffman et al., 2003; Hoffman et al., 2013; Philipp Homan et al., 2011; P Homan et al., 2012). It is a feasible and time-efficient measure to assess severity of AVH on a daily basis and to evaluate improvement of AVH severity.
Secondary		
Monitor qualitative changes in AVH during the course of the rTMS treatment.	a) the qualitative content of AVH are assessed using the BAVQ-R to monitor changes in the content of AVH.	The BAVQ-R (CHADWICK, LEES, & BIRCHWOOD, 2000) is a self-report measure of patient's beliefs, emotions and behavior about AVH. This allows to assess changes in the quality of AVH over time and monitor if severity increases to the point of being dangerous for the patient or others (suicidal or homicidal tendencies).
Assessment of AVH as part of positive symptoms.	b) positive symptoms BPRS-subscale including "Hallucinatory Behavior", "Conceptual Disorganization", "Suspiciousness", and "Unusual Thought Content".	The positive symptoms BPRS-subscale is a well validated, often in studies used measure to assess positive symptoms including AVH (Robinson et al., 2015; Shafer, 2005).
Examine the effects of rTMS on the global functioning of the patient with a schizophrenia spectrum disorder.	c) global function is assessed using the Clinical Global Impression (CGI) and the General Assessment of Functioning (GAF)	The global scores (CGI (Haro et al., 2003) and GAF (Jones, Thornicroft, Coffey, & Dunn, 1995)) nicely complement the specific measure and provide a complete picture of the patients mental state.
Confirm that rTMS has no cognitive side effects.	d) The neuropsychological test Repeatable Battery for the Assessment of Neuropsychological Status (rBANS)	In order to confirm that rTMS has no undesirable cognitive side effects the rBANS is used as a standard cognitive measure.

Neurophysiological changes using magnetic resonance imaging (MRI) are investigated as predictors for rTMS treatment response.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a randomized, placebo controlled, double-blind clinical trial. We aim to assess the efficacy of rTMS as a potentially beneficial treatment option in drug-naïve patients and patients refusing antipsychotic medication who suffer from AVH. We use a novel protocol with only one day of treatment including 4 sessions of low-frequency rTMS and compare the effects with the sham stimulation. Further, we aim to examine structural and functional neurophysiological characteristics as predictors for rTMS.

As primary outcome, we aim to examine the efficacy of low-frequency rTMS for AVH in patients with a schizophrenia spectrum disorder with regard to AVH based on the HCS. Further, Hallucination quality (BAVQ-R), hallucinations as a part of positive symptoms (BPRS-subscale), clinical global improvement (CGI), and general assessment of functioning (GAF) are secondary outcome measures Structural and functional neurophysiological characteristics (rCBF, resting fMRI, T1, and DTI) are investigated as potential predictors for rTMS treatment response.

In order to achieve these aims, we will have two intervention arms: real and sham rTMS. Patients who are willing to take part in the study and declining treatment by antipsychotic medication to sufficiently treat psychotic symptoms will be randomly assigned by the (trained) research coordinator to either sham or real rTMS.

Subjects will be randomized using a permutation block design to real rTMS or sham rTMS treatment. Accordingly, a well-documented double-blind randomization plan will be developed by the study's biostatistician and implemented in collaboration with the investigator. Copies of the resulting permutation blocks and randomization codes will be kept by the unblinded research coordinator. Blinded study personnel will not have access to these codes. When a new subject is randomized to a particular group, the research coordinator will provide written notice of the randomization condition of the subject to the operator of the rTMS.

Double-blinding is ensured by the fact that the trained research assistant who is performing the rTMS treatments is not the same person (rater) who will conduct the psychopathology assessments. This allows the unbiased assessment of changes in AVH severity due to rTMS without the prior knowledge of the rater whether the patient received real or sham rTMS.

The treatment will be offered only if clinically indicated and the benefits of procedure outweigh risks. Therefore, participating in the study does not introduce additional risks to the patient other than the risks which are already present because of the clinical care.

rTMS is a non-invasive procedure with the most common side effect being headache or pain, which is transient and responds well to combination of acetaminophen and ibuprofen (we will administer if patients require so). If local scalp pain or face muscle pain occurs, adjustment of the coil usually alleviates the pain. There are no known mechanisms through which the induced magnetic field produced during TMS stimulation could generate biological adverse effects in the absence of extraneous implanted metal in the skull or brain. That is the reason we will exclude all patients with metal implants (they would not be eligible because of the MRI component either). The most significant safety concern is seizure, however, as can be seen from Table 3, 1Hz rTMS for 1800 seconds is considered safe (Rossi et al., 2009). As a safety precaution, however, we will exclude patients with seizure disorders from this study. There are no additional significant risks due to study procedures.

Recruitment will occur at the Zucker Hillside Hospital at Northwell Health. For further information on recruitment see section 5.5 "Strategies for Recruitment and Retention". Regarding data analyses, no interim analyses are scheduled at this point.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We will obtain a blood sample to assess the serum concentration of the antipsychotic at the moment of hospitalization to confirm that patients are antipsychotic-free thus eligible for this study. In the event of not having obtained a blood sample in the emergency room for an eligible patient that is willing to consent due to logistic reasons, we will obtain the specimen via venipuncture after the consent form is signed, provided that the patient did not receive antipsychotic drugs in the emergency room or inpatient unit. The specimens of individuals for whom an extra vial of blood was extracted for potential serum antipsychotic concentration analysis that later do not consent to participate in the study will be destroyed immediately without being processed.

For TMS, it is important to at least have a group that gets treated with the sham rTMS if no cross-over trial is possible and no waiting-list is planned to be included in the study.

Having matched patients in the control group compared to the treatment group allows a comparison of the two in terms of symptoms. A healthy control group would not allow such a comparison.

4.3 JUSTIFICATION FOR DOSE

Using low-frequency (LF) rTMS is thought to decrease cortical excitability. In schizophrenia, Hoffman et al. (1999) were the first to introduce rTMS for the treatment of refractory AVH in treatment-resistant patients. The authors used LF rTMS over the left temporo-parietal junction (TPJ) and showed significantly reduced AVH severity with effects lasting up to 15 weeks. Yet, daily administration of rTMS over the course of several days without antipsychotic medication could comprise risks, especially for patients suffering from additional psychotic symptoms.

Therefore, the crucial next step is, firstly, to explore the effects of rTMS in medication-free individuals in the initial phase of psychosis and, secondly, to use an accelerated protocol of only one day with four sessions of rTMS. The reduced time of rTMS administration would diminish potential risks related to other psychotic symptoms and reveal rTMS effects on AVH within a few days.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 18 to 65
4. Diagnosed with DSM V diagnosis of schizophrenia (295.90), schizoaffective disorder (295.70), or brief psychotic disorder (298.80), prone to AVH in the acute phases of the disorder

5. Willing to adhere to the rTMS regimen
6. Subtherapeutic antipsychotic serum level upon admission as per Nathan Kline Institute reference guidelines on antipsychotic therapeutic serum levels.
7. Agreement to adhere to Lifestyle Considerations (see section 5.3) throughout study duration

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Therapeutic level of antipsychotic medication
2. ECT or rTMS within three months (see the TMS screening questionnaire)
3. History of seizures
4. Presence of implanted electronic device or metal implant in the head and neck region (DBS, cochlear implant, etc.)
5. Pregnancy, as assessed with a pregnancy test prior to every MRI measurement, or lactation
6. Any active general medical condition or CNS disease which can affect cognition or response to treatment
7. Treatment with another investigational drug or other intervention within 2 weeks
8. Current diagnosis of delirium, dementia, or amnestic amnesiac disorder; Diagnosis of mental retardation; Current (within the past three months) diagnosis of active substance dependence, or active substance abuse within the past week as indicated by self-report.
9. Patients who are cognitively impaired and are thus not able to give informed consent

Note, that other medication such as antidepressant, pain killers, or sleep medication are no exclusion criteria per se. Yet, if these medications are needed for the treatment of other mental illnesses such as subsumed under point 5 or 7 of the exclusion criteria then patients cannot be included in the study.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to

- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches that are available as per standard clinical care) in the 2 hours prior to the MRI measurement on Day 1 and 3 are not allowed.
- Abstain from caffeine- or xanthine-containing products (e.g., coffee, tea, and cola drinks) for 2 hours before each imaging measurement (Day 1 and 3).
- Abstain from alcohol the evening before the start of the study until after collection of the final imaging data.

Note, that participants are not asked to abstain from antipsychotic medication if they wish to take it or in case of an emergency. Yet, no treatment with antipsychotic medication from the study´s start until completion of the study is one of the main inclusion criteria and violation of this criterion will lead to exclusion from the study. See section 2.2.1 “Known Potential Risks” for more information on risks and section 5.5 “Strategies for Recruitment and Retention” for further information on recruitment.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a no suffering from AVH may be rescreened at a later date. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

This is an exploratory pilot study to test the efficacy of rTMS for the treatment of AVH in patients with schizophrenia spectrum disorder. Thus, we aim to recruit 20 patients per group (active *versus* sham rTMS) to determine the treatment´s efficacy.

Both male and female patients with a schizophrenia spectrum disorder, who are referred for standard care treatment and who express interest in an additional day of rTMS treatment before the start of antipsychotic treatment, will be recruited for the study.

Patients will be approached by trained staff of the study and asked about their AVH symptoms. In the case that patients report hearing voices (which is not always the case), we will propose rTMS as a novel, potentially beneficial treatment option for AVH, as confirmed by meta-analysis that found significant effect sizes ranging from 0.4 to 1 depending on the publication (Aleman et al., 2007; Demeulemeester et al., 2012; Freitas et al., 2009; C. Slotema et al., 2012), compared to conventional antipsychotic medication. Especially, if the hallucinations are the symptom that predominantly cause the suffering, then rTMS may lead to symptom reduction and may have a lower risk for potential side effects than the treatment with antipsychotics.

We will not try to dissuade patients who want to take antipsychotic medication from taking medication. Our aim is to convincingly explain the advantages of rTMS as a novel treatment with a promising potential. Antipsychotic medication can be given after completion of the study or at any point during the study in the case of an adverse event (see section 8.3.4 “Time Period and Frequency for Event Assessment and Follow-up” for more information), or patients request, but that would mean termination from the study.

For recruitment, we consider all patients suffering from AVH who are not currently on antipsychotics. The patients’ history of antipsychotic medication is not in the focus. We will include patients with a first-episode psychosis, patients who did have antipsychotic medication in the past, patients who decline antipsychotic medication.

Recruitment will occur at The Zucker Hillside Hospital from the inpatient unit at Northwell Health. The Zucker Hillside Hospital is the major psychiatric facility associated with the health system. Subjects will be recruited from the inpatient and outpatient units. Prospective subjects will be approached for study enrollment by the psychiatrists who participate in this study and/or a research fellow. Upon subject’s agreement, a meeting with the research staff will be scheduled to begin the informed consent process.

The consent process begins with an assessment of the patient’s ability to give informed consent. Patients who on initial evaluation by the study investigator are deemed not to be capable of giving informed consent will not be evaluated further. Patients who are deemed capable of giving informed

consent will then be provided with a full and complete description of the study. Capacity will be determined by treating physician prior to the consent process. The capacity assessment will be a brief form checked and signed by the physician who is treating the subject. This form will be kept in the study chart of each subject. The patient will be provided with ample opportunity to review the consent and have all their questions addressed prior to completing enrollment. Written consent will be obtained prior to the commencement of study procedures.

Consent will follow IRB approved procedures. Consent will be obtained by the PI, Dr. Philipp Homan, the study's MD, Dr. Miklos Argyelan, and the study coordinator, Stephanie Winkelbeiner. Consent for patients will occur on the inpatient units of the Zucker Hillside Hospital at MRI.

In order to ensure that subjects understand the fundamental aspects of the study, we require that they demonstrate this by correctly answering a series of specific questions about the study covering key aspects of the study. These Study Information Reviews are IRB approved. The format of the Study Information Review is a question followed by two possible answers. The answers are written in a parallel sentence structure to minimize reading difficulty. We employ the parallel answer format instead of a true false format because of our experience that subjects with limited education and test taking skills better comprehend the parallel answer format.

An example of part of a Study Information Review is presented below.
DIRECTIONS: Below are questions that people frequently have about the study. Each question is followed by 2 answers. One answer is correct and the other answer is wrong. Please put a check mark next to the correct answer.

Question 1. Do I have to be in the study to get treatment at the hospital?

a) To get treatment, I must be in the study.
OR
b) To get treatment, I do not have to be in the study.

Question 2. If I start in the study, can I leave before it is over?

a) If I decide to be in the study, I must stay until it is over.
OR
b) If I decide to be in the study, I can leave any time that I wish.

Question 3. How long does the study last?

a) If I want to, I may be in the study for up to 3 days.
OR
b) If I want to, I may be in the study for up to 3 weeks.

Subjects must answer correctly all the questions on the Study Information Review before providing informed consent for the study. Informed consent will be documented when the subject signs the consent form that has been approved by the Institutional Review Board.

The study purpose, procedures, risks, benefits, and alternatives will be discussed. After informed consent is signed, eligibility will be confirmed by diagnostic and psychometric assessments by trained raters as described in the screening visit. Additionally, we will measure blood levels of antipsychotics to confirm that patients are antipsychotic-free.Based on our previous experience in enrolling patients in other trials, we anticipate that we can accomplish the recruitment goal of forty patients over the course of one year in the proposed study.

Patients will be paid $ 120 in total for their time and travel expenses for being in this study. If they do not complete the entire study, they will be paid for the number of completed visits. Payment will be made at the end of the study or when patients end their participation.

If the total payment received from Northwell Health, during this year, is equal to $600 or more, the payment is required to be reported to the IRS. Although this study does not pay $600, if patients participate in other Northwell Health studies, it is possible their payment could end up totaling $600. If this occurs, the payment received on this study will be reported to the IRS. In this case, patients will be issued a 1099 form and be required to provide their social security number at that time for reporting purposes. Patients will also be responsible for reporting this income while filing your tax return.

Compensation

	Screening Day	Baseline Assessment	Treatment Day	Follow-up Assessment
Visits	Visit 1	Visit 2	Visit 3	Visit 4
Procedures				
rTMS	None	None	Any weekday	None
MRI	None	1st at baseline	None	2nd after rTMS
Clinical Assessment & blood work	Yes	Yes	Yes	Yes
Compensation	$20	$50	$0	$50

Note that the Screening Day is not specifically set. This day can either be on the first day of the study such that patients who are willing to participate could start immediately with the baseline measurements. While patients who are for example recruited in the evening would have their first day of the study on the following day. In the special case of enrollment on a Friday, the start of the study would be the following Monday. Thus, patients would have to declare that they do not want to take antipsychotics during the weekend and the time of the study. See section 2.3.1 “Known Potential Risks” for information.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

For the treatment of the auditory verbal hallucinations (AVH), we will use transcranial magnetic stimulation (TMS). Magnetic stimulation is a non-invasive technique used to excite and depolarize neurons in the brain and peripheral nervous system using induced currents. The excitation is caused by weak electric currents induced in the tissue by rapidly changing magnetic fields. The discovery is based on the principle of electromagnetic induction – discovered in 1831 by British scientist Michael Faraday.

When used to stimulate the brain it is normally referred to as TMS. TMS can be either single or paired pulse TMS or repetitive TMS (rTMS). Single/paired pulse TMS is mainly used for physiological research and diagnostic purposes. When the magnetic stimulation is delivered at regular intervals, it is termed rTMS. When stimulating the brain rTMS can produce lasting effects on cerebral functions, such as improvement of mood in depression (George and Belmaker, 2007).

Our TMS stimulator was manufactured by Magventure and fulfills the following quality assurances that can be found on their website (https://www.magventure.com/en-gb/About/Quality-Assurance):

> "All products are developed and manufactured in accordance with the standard ISO 13485:2003, the current EU Medical Device Directive, the Canadian Medical Devices Regulation (CMDR), US 21 CFR 820 for the USA, and in accordance with a number of additional country-specific regulations. MagPro stimulators and magnetic coils are approved as medical devices in Europe, the USA, Canada, China, Japan, South Korea, Australia, Russia, and other markets worldwide."

That model that is used in our institute is the MagPro X30. This model is described to be "an advanced, high performance magnetic stimulator designed primarily for research purposes" with "a high quality tool for researchers with a large choice of stimulating parameters" and that has "stimulation rates up to 100 pps at high intensities and the possibility to combine waveforms and pulse modes" (https://www.magventure.com).

Auditory hallucination is the false perception of sounds. A common form involves hearing one or more voices, which is often associated with psychotic disorders such as schizophrenia. Despite intensive treatment with antipsychotic medication, the auditory hallucinations often persist.
It is anticipated that approximately 75 % of people diagnosed with schizophrenia experience AVH. Though, not all auditory hallucinations are associated with mental illness.

According to research, the AVH might occur as a result of over-activation of the left temporo-parietal cortex, which is the part of the brain responsible for speech perception (Rosenberg, Roth, Kotler, Zangen, & Dannon, 2011). Research indicates that rTMS is able to alter neural activity over the temporo-parietal cortex. Studies have shown that when rTMS is used as an adjunct to antipsychotic medication in treatment-resistant cases, the frequency and severity of auditory hallucinations can be reduced (Waters, Woodward, Allen, Aleman, & Sommer, 2010).

On clinicaltrials.gov it is possible to follow the development of ongoing clinical trials for treating auditory hallucinations disorder with rTMS. Treatment of auditory hallucinations with rTMS has not yet been approved by a regulatory body, and the treatment is considered investigational. Thus, we aim to test the efficacy of rTMS as a treatment for AVH in schizophrenia.

6.1.2 DOSING AND ADMINISTRATION

All patients receive 1Hz of rTMS over the area Spt four times on 1 day (1 pulse/second and a total of 1'000 pulses: 16 minutes' protocol at 100 % of motor threshold modified based on Hoffman et al.(Hoffman et al., 2003)). Area Spt will be localized via baseline structural imaging and our Localite TMS navigation system. Subjects will be withdrawn from the study if side effects become limiting, or if either the patient or principal investigator determine that rTMS should be discontinued.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

TMS

The study's treatment will be performed with the TMS device of our institute at the Zucker Hillside Hospital. The procedure will be monitored by an MD and performed by trained staff.

Blood samples

The sample will be processed to extract the serum, which does not contain DNA, and plasma and residual samples will be immediately destroyed. The serum sample identified by the investigator generated unique identification number – hence not containing any PHI – will be sent to The Tom Cooper laboratory, Nathan Kline Institute, Orangeburg, New York.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Blood samples

Each subject will be assigned a unique identification number generated by the research staff, and data will be coded using this number. The coded link to subjects' identities will be kept separate from the database in a locked file accessible only to the principal investigators. Hard copies of data will be stored in locked files in secure offices.

6.2.3 PRODUCT STORAGE AND STABILITY

TMS

The TMS device is stored in a lockable room and only used by trained staff.

Blood samples

The specimens of individuals for whom an extra vial of blood was extracted for potential serum antipsychotic concentration analysis that later do not consent to participate in the study will be destroyed immediately without being processed.

6.2.4 PREPARATION

Blood samples

The Tom Cooper laboratory, Nathan Kline Institute, which has extensive reputation in the field, will analyze the serum samples to obtain serum levels of Risperidone, Paliperidone, Olanzapine, Aripiprazole, Quetiapine, Ziprasidone, Lurasidone, Haloperidol, Fluphenazine, or Perphenazine (depending on relevance) using a validated liquid chromatographic method developed by the Cooper laboratory.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Patients who are willing to take part in the study and declining treatment by antipsychotic medication to sufficiently treat psychotic symptoms will be randomly assigned by the (trained) research coordinator to either sham or real rTMS following a permutation block randomization plan. The research coordinator

responsible for the randomization of patients, Stephanie Winkelbeiner, will be unaware of what the next treatment assignment will be. Using this method of "concealed allocation of treatment assignment" ensures an unbiased randomization process. Double-blinding is ensured by the fact that the trained research assistant who is performing the rTMS treatments is not the same person (rater) who will conduct the psychopathology assessments. This way double-blinding is ensured in the sense that the rating is not influenced by the knowledge about the intervention arm (real or sham rTMS arm). This allows the unbiased assessment of changes in AVH severity due to rTMS without the prior knowledge of the rater whether the patient received real or sham rTMS. Patients declining medication will be randomly assigned to either the sham or the real rTMS group. For more detailed information on randomization see section 4.2.

For sham rTMS, the coil will be tilted by a 45-degrees angle. This procedure does not induce neuronal changes in the brain but still gives makes the characteristic noise produced during real rTMS stimulation.

Unblinding will only occur in the case of a serious adverse event or if patients wished to know after study completion in which study arm they have been. Unblinding will have to be approved by the PI first and can be done by the PI or the study coordinator.

6.4 STUDY INTERVENTION COMPLIANCE

Compliance to study intervention is firstly confirmed by the patient signing the informed consent form. If patients do not want to continue treatment and finish all 4 rTMS sessions together with pre- and post-imaging and interviews, they will be excluded from the study which will be mentioned in the case report form. The data collected up to this point will not be included in the analysis because the primary outcome is the outcome measure of the HCS for which all three measures (baseline, after the last rTMS session, post-MRI) are necessary to reasonably estimate the symptom trajectory.

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE MEDICINE

N/A

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from rTMS does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline indicated by a score of 3 ("mild") or less for all four items of the positive symptom BPRS-subscale (Robinson et al., 2015)) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation
- Positive symptoms BPRS-subscale rating
- BAVQ-R rating
- MRI measurements

The specimens of individuals for whom an extra vial of blood was extracted for potential serum antipsychotic concentration analysis that later do not consent to participate in the study will be destroyed immediately without being processed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. Nevertheless, subjects may be prematurely terminated from the study if the investigators assess that the subject's clinical condition requires treatment(s) not available within the study context.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy as assessed with a pregnancy test before the two MRI measurements
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive rTMS 4 times for one day
- If patients experience side effects that they are not willing to endure (such as headaches for example)
- Any medical condition which requires treatment with a medication with psychotropic effects
- Significant risk of suicidal or homicidal behavior (including aggressive behavior towards staff, others or themselves)
- MR Imaging contraindications
- Moving of patient or end of status as an in-patient at the Zucker Hillside Hospital

Duration of non-compliance will be determined by the trained study coordinator. Patients will be monitored closely be the study coordinator and all trained staff of the study. Changes i.e. in medication will be assessed before every visit/intervention.

If the patient had to have antipsychotics given because of an emergency or worsening of psychotic symptoms, then they are terminated from the study. However, we will also communicate on the ward that the patient's well-being is of main concern. Thus, should a patients' condition worsen and antipsychotics are thought to be the best help than medication should always be given regardless of the patient being enrolled in the study.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not

receive the study intervention may be replaced. Subjects who sign the informed consent form, are randomized, receive the study intervention, subsequently withdraw or are withdrawn or discontinued from the study will be replaced.

7.3 LOST TO FOLLOW-UP

N/A

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Raters

All assessments will be performed by trained raters.

Time frame

Screening procedures / evaluation must be done on the same day or the day before inclusion of the patient into the study. The reason for this is that we assess rTMS effect independently of potentially influencing antipsychotic medication effects. Therefore, patients cannot start with antipsychotic medication treatment parallel to the rTMS treatment. Clinical interviews will be conducted by trained staff.

Imaging

MRI acquisition will consist of the following: On the day of imaging, the patient will be transported to the North Shore University Hospital 3T Siemens Prisma MRI suite. The patient will undergo an approximately 55 minutes long acquisition session. All subjects will receive structural (e.g., T1) and functional (e.g. resting BOLD fMRI, DTI, and ASL) MRI exams. During the anatomical images, the participating subject will be asked not to move, during resting state fMRI, the subject will be asked to open their eyes and to think of nothing in particular, but to stay awake. The total scanning time will be approximately 55 minutes.

Assessment of instruments

The primary outcome measure is the improvement of AVH measured with the HCS.

The secondary outcome measures are:

- Qualitative outcome of the BAVQ-R
- AVH as part of positive symptoms measured with the respective BPRS-subscale
- Global functioning assessed using the CGI and GAF
- Cognitive functioning assessed using the rBANS

Structural and functional neurophysiological characteristics are investigated as predictors for rTMS treatment response.

Outcome criteria

Responder criteria:

a. Clinically significant improvement is defined as a score of <8 on the HCS (Hoffman et al., 2013)
b. Drop-outs: defined as patients who discontinue treatment before completing the 4 rTMS sessions.

Premature exits:

a. Consent for study participation is withdrawn before 4 rTMS treatments have been administered, or
b. rTMS is discontinued for clinical or other reasons before 4 rTMS have been administered, or
c. Patient misses more than two treatments in total.

Both drop-outs and premature exits in this study will be analyzed as last observation carried forward.

8.2 SAFETY AND OTHER ASSESSMENTS

TMS

The treatment will be offered only if clinically indicated and the benefits of procedure outweigh risks. Therefore, participating in the study does not introduce additional risks to the patient other than the risks which are already present because of the clinical care. rTMS is a non-invasive procedure with the most common side effect being headache or pain, which is transient and responds well to combination of acetaminophen and ibuprofen (we will administer if patients require so). If local scalp pain or face muscle pain occurs, adjustment of the coil usually alleviates the pain. There are no known mechanisms through which the induced magnetic field produced during TMS stimulation could generate biological adverse effects in the absence of extraneous implanted metal in the skull or brain. That is the reason we will exclude all patients with metal implants (they would not be eligible because of the MRI component either). The most significant safety concern is seizure, however, as can be seen from Table 3, 1Hz rTMS for 1800 seconds is considered safe (Rossi et al., 2009). As a safety precaution, however, we will exclude patients with seizure disorders from this study. There are no additional significant risks due to study procedures.

MRI

Precautions to minimize MR risks have been described above. Briefly, disposable earplugs or non-magnetic headphone sets will be used for all participants to minimize the risk associated with acoustic noise levels. To minimize risks related to the magnetic field, our facility incorporates a complete range of procedures to assure security of the restricted access area, and careful screening of potential subjects, before they enter the restricted access area. The system will be operated within limits already determined not to pose significant risk to humans. Proper and routine monitoring of all radio frequency electronics (e.g. coils, transmitters, system security, etc.) will be performed on a regular basis to minimize the risks associated with Specific Absorption Rate (SAR). Incidental risks are minimized by an extensive set of safety checks employed by our facility prior to scanning. Claustrophobia from magnetic resonance imaging will be reduced by explaining the nature of the scanner in detail to all participants prior to enrollment and allowing them to become acclimated to the procedure by using a mock scanner. Subjects who have a history of significant claustrophobia will not be entered into the study and if it occurs, the study will be terminated at the subject's request. All subjects undergoing MR imaging will be provided with a “squeeze ball” that will alert the operator when the subject has a problem that needs to be addressed or wants to terminate the exam.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include seizures that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs), not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be

pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The PI as well as the research coordinator assisting the PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Thus, in the case of a worsening of symptoms leading to a worsening of the patient's condition, antipsychotic medication can be given on the ward if the responsible MD thinks that this is necessary for the patient's health. Patients' well-being is the main priority even if this means the termination from the study because of the antipsychotic.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI as well as the research coordinator assisting the PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Side-effects will be monitored by the study physician and self-reports. Treatment side effects will be measured using the Treatment Emergent Side Effects Scale (TESS). Reported adverse events will be evaluated and treated according to standard treatments procedures. In the case of a serious or intolerable adverse event subjects will be withdrawn from the study and he will be referred for treatment if necessary. Serious adverse events will be reported to IRB in no more than 24 hours after occurrence or after the psychiatrist is informed. In addition, this study will be fully compliant with the NIMH reportable events policy.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

Pregnancy will be assessed with a pregnancy test prior to the two MRI measurements. In the case of pregnancy, participation in the study is terminated, because of potential risks of MRI measurements for pregnant women.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 5 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.]

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint(s):

H0: Real rTMS has no superior effect over sham rTMS in reducing severity of AVH in schizophrenia (HCS score).
H1: Real rTMS has a superior effect over sham rTMS in reducing severity of AVH in schizophrenia (HCS score).

Secondary Efficacy Endpoint(s):

1. H0: Real rTMS has no superior effect over sham rTMS in reducing quality of AVH in schizophrenia (BAVQ-R score).
   H1: Real rTMS has a superior effect over sham rTMS in reducing quality of AVH in schizophrenia (BAVQ-R score).

2. H0: Real rTMS has no superior effect over sham rTMS in reducing positive symptoms including AVH in schizophrenia (BPRS-subscale).
   H1: Real rTMS has a superior effect over sham rTMS in reducing positive symptoms including AVH in schizophrenia (BPRS subscale).

3. H0: Real rTMS has no superior effect over sham rTMS in reducing severity of general psychopathology in schizophrenia (CGI score).
   H1: Real rTMS has a superior effect over sham rTMS in reducing severity of general psychopathology in schizophrenia (CGI score).

4. H0: Real rTMS has no superior effect over sham rTMS in reducing global functioning in schizophrenia (GAF score).
   H1: Real rTMS has a superior effect over sham rTMS in reducing global functioning in schizophrenia (GAF score).

5. H0: Real rTMS compared to sham rTMS does not impact cognitive functioning (RBANS).

H1: Real rTMS compared to sham rTMS does not impact cognitive functioning (RBANS).

6. H0: Response to rTMS is not predicted by neurophysiological characteristics.
   H1: There are specific neurophysiological markers that predict response to rTMS.

9.2 SAMPLE SIZE DETERMINATION

This study aims to examine the efficacy of rTMS for the treatment of AVH in schizophrenia. To determine the effect of rTMS, this study uses an exploratory approach and should be considered a pilot study. If a treatment effect of rTMS (as compared to sham rTMS) would be detected, then this may serve as the basis for a follow-up study in a larger sample.

Previous meta-analyses (Aleman et al., 2007; Demeulemeester et al., 2012; Freitas et al., 2009; C. W. Slotema et al., 2014; C. W. Slotema et al., 2010; Tranulis et al., 2008) reported effect sizes ranging from 0.42 to 1.04 for LF rTMS over the left TPJ for the treatment of AVH. Based on this, we assume an effect size of 0.9 as a clinically meaningful effect to justify rTMS for the treatment of AVH compared to conventional antipsychotic medication. Following from this, we performed an *a priori* power analysis using the statistical software package R 3.1.3 and pwr.t.test (based on (Cohen, 1988)). With the assumed effect size of 0.9 and 80% power (α = 5%) we will have to recruit 40 patients in total, with 20 patients in the real rTMS and 20 patients in the sham rTMS group.

Considering the limited time frame of one year and based on the investigators' experience in the clinic about the number of subjects, we expect the aim of N = 40 to be feasible.

9.3 POPULATIONS FOR ANALYSES

Data of all patients who attended pre-MRI and interview, 4 sessions of rTMS, and post-MRI and interview will be included in the analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics will include all patients who completed the study. Patient groups (stratified according to either their sham or real rTMS treatment) will be compared concerning age, sex, socio economic status, general psychopathology (CGI, GAF), severity of AVH (BPRS-subscale, BAVQ-R), and cognitive outcome (rBANS). In particular, mean (standard deviation) together with the range (min, max) will be assessed for the two groups.

Inferential statistics: the p-value will be set to 5% and therefore every value below this threshold is considered significant. Effect sizes will be calculated as well to evaluate if we are dealing with a clinically important effect. Covariates will be included in the analyses such as age and sex.

General assumptions of heterogeneity and normality will be assessed before any subsequent analysis. Based on this either parametric or non-parametric tests will be chosen.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Our primary goal is to examine if real rTMS for the treatment of AVH is superior to sham rTMS. Therefore, we test if symptoms decreased in patients who received 4 sessions of low-frequency rTMS for one day.

For this purpose, repeated measures ANCOVAs will be implemented with time of measurements as the within-subject factor, group (treatment vs. placebo) as between subject's factor, and baseline HCS scores as covariate.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Our secondary goal is to test if rTMS improves also the quality of AVH (BAVQ-R), positive symptoms (BPRS-subscale), general psychopathology (CGI), and global functioning (GAF). Further, we want to confirm that rTMS has no impact on cognitive functions (rBANS).

Therefore, we will compute a number of repeated ANCOVAs with time of measurements as the within-subject factor, group (treatment vs. placebo) as between subject's factor, and baseline BAVQ-R scores, the positive symptom BPRS-scale, the CGI, and GAF scores as covariates, respectively. Patients who drop out of the study will not be included in the analyses. Further, we will compare the rBANS scores of baseline with the outcome scores within patients.

Additionally, we want to test if baseline neuroimaging biomarkers can predict response to rTMS. Therefore, voxel-wise multiple regression analyses in our neuroimaging measures will be performed to reveal areas and networks which correlate with the baseline scores of the HCS We will calculate structural and functional connectivity analyses.

Preprocessing, and overview of the neuroimaging measures:

Baseline metabolic neuronal activity

The treatment effect will be monitored by assessing the baseline resting metabolic neuronal activity measured by ASL (Philipp Homan et al., 2011; Kindler et al., 2012; Orosz et al., 2012). Additionally, variations in resting CBF may be used as covariates of nuisance in all the analysis steps described so far.

The perfusion images will be pre-processed and analyzed with FSL 5.0. First, the raw pCASL data undergo pre-processing that includes motion-correction with MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), outlier-detection, and removal (Jenkinson et al., 2002; Jenkinson & Smith, 2001). Second, in order to create a mean difference map for each subject, control-tag pairwise differences are computed. These maps are normalized by the equilibrium magnetization (M0) of arterial blood estimated via the magnetization of CSF. Third, Bayesian Inference for Arterial Spin Labeling MRI (BASIL) (M. A. Chappell, Groves, Whitcher, & Woolrich, 2009) is employed to calculate resting state perfusion which provides blood flow in absolute units ([ml/100g/min]) with the following parameters: BAT = 1.3, TR = 3.5, TE = 1.8, T1 (blood) = 1.65 s, and alpha = 0.85. The application of a GM mask and partial volume correction(M. Chappell et al., 2011) ensures that only GM voxels are included in the CBF calculation. Fourth, the perfusion images are spatially normalized and transformed into MNI space using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001) and FNIRT (Andersson, Jenkinson, & Smith, 2007), and then spatially smoothed with a 6 mm FWHM Gaussian kernel.

Resting state networks (RSN, BOLD fMRI)

Brain function is thought in terms of complex circuits that are optimized both for segregated and distributed information processing. These circuits can be studied with a task or at rest(Fair et al., 2007; Fox et al., 2005; Raichle & Snyder, 2007). The most studied functional connectivity network at rest is the default mode network (DMN) which may be investigated using BOLD fMRI time-series and quantified CBF time-series(Kay Jann, Koenig, Dierks, Boesch, & Federspiel, 2010; Orosz et al., 2012). In psychiatric population it may be of special interest to investigate the neurophysiological mechanism of hallucinations in patients because they do not need to actively respond to a task (i.e. resting state network/RSN). Resting-state neural activity can originate from the interplay between the local neural dynamics and the

large-scale structure of the brain (Cabral, Hugues, Sporns, & Deco, 2011). Interestingly, RSN were found to be altered in disease population as compared to healthy controls (Bassett, Nelson, Mueller, Camchong, & Lim, 2012), indicating that the quantitative assessment of RSN may be a potential method for investigating psychiatric diseases (Meda et al., 2012) including schizophrenia (Ma, Calhoun, Eichele, Du, & Adalı, 2012; Venkataraman, Whitford, Westin, Golland, & Kubicki, 2012). Of special interest for the current proposal will be the investigation of the language related functional network, also termed "working memory" or "language network"(Catani et al., 2011; Friederici, 2011; Friederici, Brauer, & Lohmann, 2011; K. Jann et al., 2012; Morgan, Mishra, Newton, Gore, & Ding, 2009).

Network connectivity is assessed through the measure of correlation coefficient (Zalesky, Fornito, & Bullmore, 2012). fMRI-BOLD image processing will be performed within SPM8 (http://fil.ion.ucl.ac.uk) and will include 3-D motion detection and correction using Levenberg-Marquarts´s least square fit for six spatial parameters, slice scan time correction through Sinc-interpolation. Co-registration of 2-D functional and 3-D structural measurements will be performed and normalization of data will lead to images in standard MNI space. All fMRI time-series will be further analyzed within the framework of Independent Component Analysis (ICA) using the Group ICA Toolbox (GIFT software) (Calhoun, Adali, Pearlson, & Pekar, 2001). We will compute subject maps (SMs) will be computed and identify temporally coherent networks (TCNs) by estimating maximally independent spatial sources. Finally, we will use a back-reconstruction method based on PCA compression and projection to estimate subject-specific SMs and TCNs for rest separately for all sessions (Erhardt et al., 2011). A subsequent t-test for the beta values corresponding to the rest and TMS condition will be computed (Arbabshirani, Havlicek, Kiehl, Pearlson, & Calhoun, 2013).

Structure of gray and white matter properties

To investigate the structural properties of GM and WM the 3D structural T1 and DTI measurements will be used. T1 images will be used to define the regions of interest (ROI) for both structural and functional connectivity analyses. The ROIs will comprise cortical regions in the STG and superior temporal sulcus (STS, Brodmann areas/BA 41, 42 and 52) and in the subcortical thalamic area (medial geniculate body of thalamus/MGB).

With regard to structural connectivity analyses, diffusion tensor images will be used to compute fractional anisotropy (FA) values for further use in a voxel-wise statistical analysis, which will be conducted using Tract-Based Spatial Statistics (TBSS)(Smith et al., 2006); part of FSL (Smith et al., 2004) (version 5.0). FA maps are created by fitting a tensor model to the raw diffusion data using the FMRIB diffusion toolbox. Subsequently, a brain extraction tool will remove all non-brain parts of the image (Smith, 2002). All subjects' FA data will be coregistered to a 1 mm × 1 mm × 1 mm Montreal Neurological Institute (MNI) standard space. This step will be performed using a non-linear registration tool FNIRT (FMRIB's Non-Linear Image Registration Tool), which uses a B-spline representation of the registration warp field (Rueckert et al., 1999). Additionally, a mean FA image will be created and thinned in order to create a mean FA skeleton that represented the centers of all tracts common to the group. A lower FA threshold of 0.2 will be used to prevent the inclusion of non-skeletal voxels (Smith et al., 2006). Each subject's aligned FA data will then be projected onto this skeleton. The resulting data will be analyzed using voxel-wise cross-subject statistics including a randomization tool, which is a simple permutation program that allows modeling and inferences within the framework of GLM-setup and is based on non-parametric inference methods (Nichols & Holmes, 2002).

Concerning functional connectivity analyses, the ROIs will be used as seed regions to compute the functional connectivity from these regions to other cortical brain regions using the Conn toolbox, a MATLAB-based cross-platform mapping software (www.nitrc.org/projects/conn). Further, GM analyses will be performed using voxel-based morphometry (VBM) (Good et al., 2001). VBM will be computed within the statistical parametric mapping (SPM8: http://www.fil.ion.ucl.ac.uk/spm/). Cortical thickness will be estimated using FreeSurfer (*http://surfer.nmr.mgh.harvard.edu*).

9.4.4 SAFETY ANALYSES

Safety endpoints will be analyzed as summary statistics during treatment.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

N/A

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol Consent_03062018.pdf.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will

have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to,

medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the SQL Server 2012 (SYKPSYCH01V). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Zucker Hillside Hospital research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Zucker Hillside Hospital.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the SQL Server 2012 (SYKPSYCH01V). After the study is completed, the de-identified, archived data will be transmitted to and stored at the SQL Server 2012 (SYKPSYCH01V), for use by other researchers including those outside of the study. Permission to transmit data to SQL Server 2012 (SYKPSYCH01V) will be included in the informed consent.

When the study is completed, access to study data will be provided through the SQL Server 2012 (SYKPSYCH01V).

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Medical Monitor
Philipp Homan, MD, PhD, Assistant Professor The Feinstein Institute for Medical Research Hofstra Northwell School of Medicine Department of Psychiatric Neuroscience 350 Community Drive Manhasset, NY 11030 phone: +1 718-470-8267 phoman1@northwell.edu	Miklos Argyelan, MD, Assistant Professor The Feinstein Institute for Medical Research Hofstra Northwell School of Medicine Department of Psychiatric Neuroscience 350 Community Drive Manhasset, NY 11030 Phone: +1 718 470-8175 Margyela@northwell.edu

Co-investigator (consenting)	Non-consenting coordinator	Non-consenting investigator
Stephanie Winkelbeiner PhD student Phone: +1 718-470-4588 Swinkelbei@northwell.edu	Andrea Joanlanne Research Coordinator Phone: +1 718-470-8898 ajoanlanne@northwell.edu	Nandita Mathur Psychometrician Phone: +1 718-470-8588 nmathur@northwell.edu Nicole Germano Psychometrician Ngermano1 @northwell.edu Andrea Joanlanne Research Coordinator Phone: +1 718-470-8898 Ajoanlanne@northwell.edu

10.1.6 SAFETY OVERSIGHT

Yet, the study duration is only set to 1 year. It might therefore be more effective to submit a progress report to the IRB after 6 months as a safety oversight.

Data Safety Monitoring Plan

1. Personnel responsible for the safety review and its frequency:
The PI will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when re-approval of the protocol is sought). During the review process, the PI will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

Either the PI, the IRB or the Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed moderate for the following reasons:
Given the now established safety and validity of the current rTMS in our prior work, we do not view the proposed study as high risk. In fact, we view the risks associated with rTMS as minimal (Rossi et al., 2009).

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator, Philipp Homan, MD PhD according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:
The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:
Serious Adverse Events: In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. Is life-threatening OR
2. Results in in-patient hospitalization or prolongation of existing hospitalization OR
3. Results in persistent or significant disability or incapacity OR
4. Results in a congenital anomaly or birth defect OR
5. Results in death OR
6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, OR
7. Adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting serious AND unanticipated AND related adverse events, anticipated adverse events occurring at a greater frequency than expected, and other unanticipated problems involving risks to subjects or others to the IRB.

The investigator will report the following types of adverse events to the IRB: a) serious AND unanticipated AND possibly, probably or definitely related events; b) anticipated adverse events occurring with a greater frequency than expected; and c) other unanticipated problems involving risks to subjects or others.

These adverse events and unanticipated problems involving risks to subjects or others will be reported to the IRB within 5 business days of it becoming known to the investigator, using the appropriate forms found on the website.

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

- All Co-Investigators listed on the protocol.
- Sponsor
- National Institutes of Health

The principal investigator (Insert Investigator Name) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

On-site monitoring will be ensured by the research coordinators and checked by the PI throughout the study targeted review of certain data endpoint, safety and other key data variables will be assured.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into SQL Server 2012 (SYKPSYCH01V), a 21 CFR Part 11-compliant data capture system provided by the Department of Psychiatric Neuroscience. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within <specify number> working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to BioMEND Program Official. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting the Department of Psychiatric Neuroscience, Zucker Hillsides Hospital.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the BioMEND has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
AVH	Auditory Verbal Hallucinations
BPRS	Brief Psychotic Rating Scale
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
rTMS	Repetitive transcranial magnetic stimulation
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
2.0	07/05/2018	Added the Edinburgh Handedness Inventory	To have an objective measure for handedness.
2.0	07/05/2018	Changed the criterion of two weeks without antipsychotics prior to study enrollment to checking antipsychotic level by means of a blood sample	Too many patients were not eligible after receiving one dose of Haldol (PRN). Checking that there is a subtherapeutic antipsychotic serum level will ensure that patients who are enrolled in the study are antipsychotic-free.

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