Effects of Transcranial Magnetic Stimulation on motor symptoms of patients with psychiatric disorders

Study Protocol/ Version 4

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1. Title of the study: Effects of Transcranial Magnetic Stimulation on motor symptoms of patients with psychiatric disorders

2. Background information of Transcranial Magnetic Stimulation (TMS)

2.1. Description and indication of TMS

Transcranial magnetic stimulation (TMS) was introduced as a non-invasive tool for the investigation of the motor cortex allowing the modulation of human cortical excitability. Furthermore TMS was used as a brain mapping tool, mostly combined with other brain mapping techniques and as a probe of neuronal networks. Its repetitive application (rTMS), with longer lasting effects, was used to study the influence on a variety of cerebral functions and tested as an add-on therapy for psychiatric disorders. Initially applied in patients suffering from major depressive disorder (MDD), it was soon tested for patients in treating auditory verbal hallucinations, negative symptoms of schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder and other mental health disorders (Slotema et al., 2011). In the last decade researchers proceeded assessing the effects of TMS on particular symptoms, e.g. cognitive disturbances or auditory verbal hallucinations (Guse et al., 2010; Slotema et al., 2011).

Although TMS triggers action potentials in cortical neurons, especially in superficial parts of the cerebral cortex using a rapidly changing magnetic field to induce brief electric current pulses (Siebner et al., 2009), its efficacy may not be restricted to the effects under the directly stimulated area, but also due to the secondary affection of subcortical areas. The various effects include the modification of cerebral blood flow, glucose metabolism and neuronal excitability in the stimulated area as well as in interconnected brain regions (Fox et al., 1997; Conca et al., 2002). Moreover, studies reported changes of synaptic potentiation and rapid dynamic alterations in gray matter density are reported (Esser et al., 2006; May et al., 2007).

A variety of methods has been used to measure the neurobiological effects of TMS on the brain. Several studies employed single photon emission computerized tomography (SPECT) to quantify changes in brain perfusion during and after TMS. The combination of TMS and positron emission tomography (PET) allowed the study of connectivity of the human cerebral cortex. Electroencephalogram (EEG) is yet another variable that can be recorded before, during or/and after TMS sessions offering unique insights into the speed of neuronal conduction within and between the two hemispheres (Paus, 1999).

Stimulation frequencies range from 'low frequency' (1 Hz) to 'high frequency' (5- 20 Hz). The application of repeated pulses at low frequencies leads to suppression of the underlying cortical activity, while high-frequency is thought to have a stimulating effect (Gershon et al., 2003; Fox et al., 2012). Although several studies failed to demonstrate statistical differences between lower and higher frequency simulation groups (Loo & Mitchell, 2005). Another critical TMS parameter is the stimulation intensity, the calculation of which is based on the motor threshold (the lowest stimulation intensity demanded to induce muscle contractions, most usually abductor pollicis brevis twitches in at least 5 of 10 consecutive trials). The effects of subthreshold rTMS appear to be more local, in contrast to suprathreshold rTMS, which results in more distant transsynaptic effects (Schutter & van Honk, 2005). The design of many TMS efficacy studies includes a sham condition, which is supposed to produce a negligible cortical stimulation. However, an important number of various sham conditions have been found to have a substantially stimulating effect on motor and premotor cortices (Loo et al., 2000; Lisanby et al., 2001). This may explain the considerable variability in effect sizes across sham controlled studies.

The implementation of TMS in human brain mapping opened up new possibilities to probe causality at the systems level of sensory, cognitive, and motor brain networks enabling its application as a reliable diagnostic tool. Quite common is the use of TMS in creating temporary, virtual brain "lesions" by reversibly disrupting the normal functioning of the targeted cortical area. The application of TMS during various experimental tasks (online TMS) enables causal inferences regarding the functional contribution of the stimulated cortex to a specific brain function to be made (Walsh et al., 1998; Robertson et al., 2000). Due to the high temporal resolution of single-pulse TMS, the latter can be moreover exploited to identify critical time intervals during which the targeted area and interconnected brain regions contribute to the experimental task (Pascual-Leone et al., 2000). Especially the contribution of combinations of TMS with neuroimaging approaches in tracing the temporospatial dynamics of causal interactions within functional brain networks has been fundamental (Siebner et al., 2009).

2.2. Reason for the dosage and dosage plan and the length of TMS trial

The effect of TMS varies and depends on the applied protocol. Stimulation studies in healthy subjects indicated the particular specificity of the dorsolateral prefrontal cortex (DLPFC), SMA and preSMA. The left DLPFC has been highlighted for its involvement in the regulation of positive and negative emotion as well as executive function. The importance of this area in cognitive functions and modulation of limbic activity may be attributed to its extensive connectivity to cortical and subcortical circuits (Schutter & van Honk, 2005; Fox et al., 2012). Alternative brain regions to stimulate include Supplementary Motor Area (SMA) and Presupplementary Motor Area (pre-)SMA (Rochas et al., 2012; Obeso et al., 2013). These brain areas are centrally involved in motor planning and processing (Goldberg, 1985; Tanji, 1994; Boylan et al., 2001) and belong to motor pathways, the alteration of which was correlated with decreased levels of motor activity in schizophrenia and MDD (Bracht et al., 2012; Bracht et al., 2013). However, the two areas are not densely interconnected and get activated during different tasks. The decidedly differentiated subcortical projections to the two areas led Akkal et al. (2007) to hypothesize that the two areas are nodes in distinct neural systems. SMA projects predominantly to primary motor cortex (Arai et al., 2012) and is more activated in movement generation and control, while pre-SMA, which is densely interconnected with regions of prefrontal cortex, is pronouncedly activated during nonmotor, cognitive tasks (Akkal et al., 2007; Lawrence et al., 2009).

TMS in Major Depressive Disorder (MDD)/Schizophrenia

The consistent findings of meta-analyses detected a significant antidepressant effect of high frequency repetitive transcranial stimulation of dorsolateral prefrontal cortex (DLPFC) (Slotema et al., 2011; Berlim et al., 2013). In schizophrenia, low frequency TMS over left temporoparietal cortex showed moderate effect in treating auditory verbal hallucinations, while left dorsolateral prefrontal cortex stimulation was used in the treatment of negative symptoms (Slotema et al., 2011).

The effect of TMS on psychomotor retardation (PR)

Previous high frequency TMS trials at DLPFC displayed significant positive effects on psychomotor performance in patients with MDD or schizophrenia. In the study of Huber et al. (2003), women with schizophrenia demonstrated a significant improvement in the Number Connecting Test performance. Hausmann et al. (2004) detected a significant effect of TMS on psychomotor performance assessed by the Trail Making Test, a dot connecting test, in patients with MDD. Furthermore, Martis et al. (2003) demonstrated that patients with MDD treated with TMS displayed a significant improvement in fine motor activity, while Baeken et al. (2010) detected a significant improvement of the psychomotor symptoms assessed by a validated rating instrument, the Depression Retardation Rating Scales (DRRS) in patients with MDD.

However, there is conflicting evidence from numerous high-frequency rTMS studies on the left DLPFC, which failed to detect effects on psychomotor function (Rollnik et al., 2000; Loo, 2001; Speer et al., 2001; Moser et al., 2002; Hoeppner et al., 2003; Fabre et al., 2004; Sachdev et al., 2005; Schulze-Rauschenbach et al., 2005; Avery et al., 2006; Ulrich et al., 2012; Schrjivers et al., 2012). The heterogeneity of findings is probably due to heterogeneous assessment methods and study samples. Next, studies are required to disentangle pathophysiologic mechanisms of psychomotor retardation in schizophrenia and MDD. Furthermore, potentially effective TMS stimulation protocols need to be tested. Thus, we aim to test the short-

term effects of three different active TMS protocols and one sham protocol on psychomotor retardation applying different TMS locations and stimulation modes.

TMS Protocol

Patients with psychomotor retardation will be randomly assigned to four groups receiving sessions of TMS of different stimulation parameters in order to test pathophysiologic mechanisms underlying psychomotor retardation. The choice of stimulation parameters is based on protocols of previous studies with highly beneficial findings. The accurate definition of the location of the stimulation sites will follow the 10/20 System (Jasper, 1958), an international method serving primarily the application of Electroencephalography (EEG). The use of the 10/20 system for the placement of TMS electrodes is common among TMS studies (Herwig et al., 2003; Schutter & van Honk, 2006; Griskova et al., 2007). In all cases stimulation will be delivered using a figure eight coil, except sham condition where a placebo coil, identical to the normal coil will be used. The four different stimulation conditions include:

1) 15 Hz left dorsolateral prefrontal Cortex (DLPFC) repetitive TMS. Twenty 5-s trains with a 60-s interval between, giving 1500 TMS pulses per session at intensity 100% of the active motor threshold (AMT). TMS will be delivered using a figure-eight coil. As mentioned above, there is a considerable number of previous high frequency TMS trials at this site with significant effects on the psychomotor performance (Huber et al., 2003; Hausmann et al., 2004; Martis et al., 2003; Baeken et al., 2010). The rTMS protocol that will be used derives from the study of Hernández-Ribas et al. (2013), which detected a significant antidepressant effect of high frequency TMS over DLPFC.

2) 1 Hz SMA/ pre- SMA rTMS. A single continuous session with 1,000 pulses was performed at intensity 110% of the AMT using a circular coil (approximate duration 17 minutes). Low frequency rTMS has been demonstrated to decrease motor cortex excitability, the motor consequences of which are still to be unraveled. Moreover, low frequency rTMS has shown a highly beneficial effect on motor symptoms in patients with Parkinson Disease (PD) (Shirota et al., 2013). We will use the stimulation protocol of the study of Shirota et al. (2013).

3) Supplementary Motor Area (SMA)/ Presupplementary Motor Area (pre-)SMA intermittent Thetaburst Stimulation (iTBS). Three pulses of stimulation are given at 50 Hz, 80% of AMT, repeated every 200 ms. 2 s trains are repeated every 10 s for a total of 190 s (600 pulses, 200 seconds). iTBS is a modality of stimulation eliciting an excitatory effect on cortical excitability, applied primarily in patients with multiple sclerosis or post-stroke implications with beneficial findings. The findings of studies assessing the effect of iTBS over SMA on psychomotor performance in healthy individuals and patients with Parkinson Disease have been encouraging (Dusek et al., 2011; Ilic et al., 2012). We will apply the widely used protocol of the study of Huang et al. (2005).

4) Sham stimulation over occipital cortex. In this group a placebo coil, similar to the real one will be used. According to the review of Loo et al. (2000) sham conditions including various coil positions have displayed a significant effect in many cases. Based on these findings, we chose to use a placebo coil over a different stimulation area expecting a negligible stimulation effect.

The MagVenture TMS device that will be used is CE-marked for use in patients (CE 0543). Regardless of the type and the frequency of TMS, the stimulation protocol will consist of 15 daily sessions during a 3 week period.

3. Objectives and purpose

Summary of the project

Background Motor symptoms are common among schizophrenia and affective disorders and may have significant clinical and therapeutic implications. Transcranial magnetic stimulation (TMS) was introduced as a non-invasive tool for the investigation of the motor cortex allowing the modulation of human cortical excitability, as it triggers action potentials in cortical neurons using a rapidly changing magnetic field to induce brief electric current pulses (Siebner et al., 2009). Its secondary effects include modification of cerebral blood flow and glucose metabolism in the stimulated area as well as in interconnected brain regions (Fox et al., 1997; Conca et al., 2002). Despite the widely accepted inclusion of TMS in the toolbox of psychiatric treatment methods, little is known about the effect of TMS sessions on motor abnormalities.

Aim The aim of the study is to investigate the effect of TMS at different brain areas on motor functioning in patients with schizophrenia or major depressive disorder (MDD) displaying motor abnormalities. The areas we chose to stimulate, based on an extensive body of research, include Dorsolateral Prefrontal Cortex (DLPFC) and Supplementary Motor Area (SMA)/ Presupplementary Motor Area (pre-) SMA.

Hypothesis We hypothesize that patients with motor abnormalities receiving different configurations of TMS will demonstrate an improvement of motor performance. Across diagnoses, patients with motor retardation will benefit from inhibitory stimulation over SMA/preSMA.

Methods The study design is a single site four arm randomized, sham-controlled trial to unravel the pathophysiology of psychomotor retardation. 80 patients with reduced psychomotor performance will be randomly assigned to four groups (20 patients per group) receiving sessions of TMS of different stimulation parameters. One of the groups will receive sham stimulation. Regardless of the type and the frequency of TMS, the stimulation protocol will consist of 15 daily sessions during a 3 week period.

The four different stimulation conditions include: 1) 15 Hz left dorsolateral prefrontal Cortex (DLPFC) repetitive TMS. 2) 1 Hz SMA/ pre- SMA rTMS. Low frequency TMS has been demonstrated to decrease motor cortex excitability, the motor consequences of which are still to be unraveled. 3) Supplementary Motor Area (SMA)/ Presupplementary Motor Area (pre-)SMA intermittent Thetaburst Stimulation (iTBS). iTBS is a modality of stimulation eliciting an excitatory effect on cortical excitability. 4) Sham stimulation over occipital cortex using a placebo coil, similar to the real one will be used.

Outcome will be evaluated as improvement in gross motor behavior (actigraphy, SRRS), fine motor function (finger tapping test), and hand gesture

performance (TULIA). In addition, patients will be assessed with the Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960), Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) Beck Depression Inventory (BDI) (Beck et al., 1961), Positive and Negative Syndrome Scales (PANSS) (Kay et al., 1987) and Scales for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013) and Bush Francis Catatonia Rating Scales (Bush et al.,1996). Clinical ratings will be assessed at baseline and after the last TMS stimulation by a rater blinded to stimulation protocol. Statistical analysis will comprise ANOVAs of motor variables and stimulation mode as between subject variable.

3.1. Background, reason for the study and objective of the study

Psychomotor retardation (PR) is according to the Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-5), defined as an '*a visible generalized slowing of movements and speech*'.

The occurrence of PR is in psychiatry appears to be of central significance across a spectrum of mental disorders such as schizophrenia and depression subtypes, in which the planning and the execution of movements is affected, resulting to disturbances in main psychomotor domains such as fine and gross motor activity and speech (Morrens et al. 2007; Schrijvers et al., 2008).

Psychomotor symptoms have also been reported in patients with chronic abuse of cannabis (King et al., 2011), chronic fatigue syndrome (Eede et al., 2011), PTSD (Peleikis et al., 2012), while they may also be elicited by psychopharmacological agents (Casey, 2006). The occurrence of PR seems to affect the everyday life of patients since it is strongly associated with poorer quality of life (Muslimovic et al., 2008) and it may have a restraining effect on common physical activities of patients as walking (Putzhammer et al., 2005; Schrijvers et al., 2008).

Psychomotor retardation (PR) in patients diagnosed with major depressive disorder (MDD)

PR is considered to be a primary behavioral disturbance in all affective disorders (Widlocher, 1983; Parker et al., 1994). Schrijvers et al. (2008) concluded that PR is a strong diagnostic marker for melancholic depression. According to the same review, PR may have a diagnostic role in the discrimination between unipolar and bipolar depression. In fact, PR is consistently more frequent in patients diagnosed with a bipolar depression compared to unipolar depression (Akiskal, 2000; Bowden, 2005; Benazzi & Akiskal, 2008; Mitchell et al., 2008; Calugi et al., 2011; Faurholt-Jepsen et al., 2012).

The higher occurrence of PR in patients diagnosed with affective disorders with melancholic features, although disputed (Schrijvers et al., 2008), may be explained by the association of the degree of severity of the illness with both the frequency of the melancholic subtype and the occurrence of PR (Knapen et al., 2012; Terziivanova & Haralanov, 2012; Caldieraro et al., 2013,); patients with severe forms of depression report more often motor abnormalities (Cagligiuri & Ellwanger, 2000; Callugi, 2011).

Despite the great number of studies assessing the prognostic role of the PR regarding treatment response, results have been contradictory. The effect of different antidepressive drugs differs between studies. Preliminary evidence suggests TCAs to have a beneficial short-term effect on psychomotor performance in depressed patients

reporting PR (Schrijvers et al., 2008). Regarding the use of SSRIs, the same review (2008) demonstrated a significant improvement of psychomotor symptoms, with sertraline being more effective than fluoxetine (Sechter et al., 1999). The prognostic value of PR regarding the response to electroconvulsive therapy (ECT) has to be further evaluated, as the findings are inconsistent (Sobin & Sackheim, 1997).

Concerning the course of the psychomotor symptoms improvement of PR is usually accompanied by clinical response (Sabbe et al., 1996; Schrijvers et al., 2008; Douglas et al., 2011; Lee et al., 2012).

Neurophysiological substrates of PR in major depressive disorder (MDD)

Psychomotor retardation in patients with MDD has been attributed to hypodopaminergic states, particularly in the basal ganglia (Hickie et al., 1999; Videbech, 2000; Martinot et al., 2001; Schrijvers et al., 2008; Walther et al., 2012). The central role of basal ganglia in psychomotor symptoms in MDD remains a consistent finding also among neuroimaging studies (Sobin & Sackheim, 1997; Lohr & Caligiuri, 2006; Loo et al., 2008; Buyukdura et al., 2011). Apart from the decreased dopamine turnover, another very common finding in these patients is the dysfunction of prefrontal subcortical circuits and hippocampus (Hickie et al., 1999; Videbech, 2000; Martinot et al., 2001; Cheng et al., 2010; Halvorsen et al., 2012).

Studies investigating regional cerebral blood flood (CBF) in depressive patients with PR detected reduced CBF in dorsolateral and left prefrontal cortex, angular gyrus, and the anterior cingulate (Mayberg et al., 1994; Narita et al., 2004; Videbech et al, 2002; Buyukdura et al., 2011). Walther et al. (2012a) demonstrated a positive association of motor activity with perfusion in resting state in the right orbitofrontal and an inverse one in the left supplementary motor area in patients with MDD. Findings differed in healthy controls with associations detected in left caudal cingulated zone and in the right external globus pallidus.

Walther et al. (2012b) were the first to study the motor activity levels in patients with MDD with regard to white matter integrity. Findings indicated that white matter integrity in patients was not related to motor activity underneath the right dorsal premotor cortex in contrast to controls. In patients, significant associations were detected in the posterior cingulum, underneath the left primary motor cortex and the left parahippocampus gyrus. In a similar study, Bracht et al. (2013) found an association across the pathway between right rostral anterior cingulate cortex and the pre-supplementary motor area.

PR in patients with schizophrenia

A wide range of various psychomotor symptoms have been studied in patients with schizophrenia spectrum disorders. However, a commonly accepted symptom definition is still not available (Walther & Strik, 2012). Among studies, motor symptoms have been described as parkinsonian symptoms, catatonic symptoms, reduced motor drive, neurological soft signs and various dyskinesias (Walther & Strik, 2012).

The correlation of motor abnormalities, negative symptomatology and cognitive deficits in schizophrenia is a consistent finding among studies (Wolff & O' Driscoll, 1999; Farrow et al., 2005; Morrens et al., 2007; Walther et al., 2009; Bervoets et al., 2013). However, Wolff & O' Driscoll (1999) mentioned that the methods assessing these symptoms need to be more sensitive as a reduction of psychomotor activity levels is sometimes recognized as negative symptoms (Morrens et al., 2007).

PR may antecede the appearance of psychotic symptoms according to Gschwandtner et al. (2006), who demonstrated as well that psychomotor function in individuals at high risk for schizophrenia was significantly worse in comparison to risk-free controls, a finding that replicated the findings of a study of the neuromotor development during the childhood of adults diagnosed with schizophrenia (Walker et al., 1996).

Regarding the effect of medication on PR, typical neuroleptics do not present an improvement according to the review of Morrens et al. (2007), while Hoothoofd et al. (2008) demonstrated no differences between Risperidone and Haloperidol. Walther et al (2010) noticed that patients treated with olanzapine had higher motor activity during the day compared to patients treated with risperidone, which may be connected to the frequent occurrence of extrapyramidal side effects in patients treated with risperidone (Leucht et al., 2009).

Neurophysiological Substrates of PR in Schizophrenia

Reduced blood flow in various brain regions and specifically in prefrontal cortex of patients with schizophrenia is a consistent finding in literature. Walther el al. (2011) detected a linear association between CBF in the right ventral anterior nucleus of the thalamus in healthy subjects that was missing in schizophrenia patients. In patients but not in controls, motor activity was correlated with CBF in the SMA, the cingulate motor area and the DLPFC. It was hypothesized that in schizophrenia cortical motor areas may compensate for insufficient basal ganglia motor output.

Motor activity levels were associated with the volumes of anterior cingulate cortex (ACC) (Farrow et al., 2005).

Walther et al. (2011) were furthermore the first to demonstrate a significant correlation between reduced motor activity and white matter ultrastructure underneath the primary and secondary motor cortex but only in schizophrenia patients. These findings were corroborated by structural connectivity analyses. Bracht et al. (2013) found that motor activity in controls was related to connection probability in thalamocortical (primary motor cortex) and striato-cortical (pre-SMA-pallidum) connections. In schizophrenia patients instead, motor activity was associated with the connection probability of preSMA-SMA connections. Thus, impaired subcortico-cortical interaction was suggested to contribute to psychomotor retardation in schizophrenia.

To sum up the findings, basal ganglia output and interaction with the cortical motor areas seems critical for motor functioning in MDD and schizophrenia. Cortical areas of interest that may easily targeted by TMS are the preSMA, SMA proper and the DLPFC. Results of imaging studies suggest these areas to have aberrant function and connectivity in MDD and schizophrenia, particularly in those patients with psychomotor retardation. It thus appears plausible that stimulation of these areas might alter the motor loop function.

Assessment methods of PR

The study of the psychomotor function has focused on a cluster of symptoms regarding domains such as gross or fine motor activity, body movements, speech, motor response time and gesture performance.

Gross motor performance One of the commonly used rating scales for the assessment of psychomotor function Salpêtrière Retardation Rating Scales (SRRS) evaluates gait, gross and facial motorics, speech and cognitive elements (Widlöcher &

Ghozlan, 1989). The gross motor activity will be furthermore assessed by actigraphs. Actigraphy is a method of quantitative assessment of motor behavior. Patients wear continuously a wrist actigraph, which records the gross motor activity in naturalistic settings. The baseline screening of patients for motor abnormalities will be based on ratings of Bern Psychopathology Scales (BPS), a validated quantitative and qualitative scales for the assessment of system-specific psychotic symptoms of three main domains: motor behavior, language and affectivity.

Fine motor performance The assessment of fine motor performance is based on a finger tapping test, during which, participants are asked to tap their index finger against their thumb as fast as possible in ten seconds. After a short period of practice, three periods will be measured and videotaped. An analysis of the tapping is additionally conducted in slow motion (Barkemeyer et al., 1998).

Gesture Performance The Test of upper limb apraxia (TULIA) (Vanbellingen et al., 2010) is a standardized examination of gesture performance that covers both pantomime and imitation domains and multiple semantic features.

Rationale and aim of the study

Psychomotor retardation is often reported by patients diagnosed with schizophrenia or MDD. Various brain regions may contribute to psychomotor slowing, but the pathophysiology still remains unclear. The effect of TMS of various stimulation parameters at different stimulation sites may lead to improved motor performance. Across diagnoses, patients with motor retardation will benefit from inhibitory stimulation over SMA. Taking into account findings of previous studies, the aims of the study are

a. To assess the effects of the 3 weeks of daily TMS sessions on motor performance in patients with schizophrenia or MDD (fine motor activity, gross motor activity and gesture performance).
b. To compare the psychomotor symptoms improvement between different TMS protocols
c. To assess the effect of daily TMS in different configurations on other non-motor symptoms e.g. depressive symptoms, negative symptoms.

3.2. Research Questions, study population

Research Questions

We aim to investigate the effect of TMS in various configurations on psychomotor retardation in patients diagnosed with MDD or schizophrenia. Diagnoses will be given following application of Mini-International Neuropsychiatric Interview (MINI)(Sheehan et al., 1998) and review of the complete cases files The study consists of a single site four arm randomized, sham-controlled trial. In total, 80 patients will be randomly assigned to four groups (20 patients per group) receiving sessions of TMS of different stimulation parameters. Sham stimulation will be administered in one group. Regardless of the type and the frequency of TMS, the

stimulation protocol will consist of 15 daily sessions during a 3 week period. The four different stimulation conditions have been described above.

Outcome will be evaluated as improvement in gross motor behavior (actigraphy, SRRS), fine motor function (finger tapping test), and hand gesture performance (TULIA). In addition, changes may be demonstrated by the Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960), Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) Beck Depression Inventory (BDI) (Beck et al., 1961), Positive and Negative Syndrome Scales (PANSS) (Kay et al., 1987) and Scales for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013) and Bush Francis Catatonia Rating Scales (Bush et al.,1996). Clinical ratings will be assessed at baseline and after the last TMS session by a rater blinded to stimulation protocol. Statistical analysis will comprise ANOVAs of motor variables and stimulation mode as between subject variable. Clinical response will be defined as a 30% reduction of the SRRS scores. Frequency of response will be compared between groups using Chi^2-Tests.

Study Population

80 in- and outpatients with schizophrenia or major depressive disorder according to DSM-5 displaying reduced levels of motor activity. Diagnoses will be given following application of MINI and review of the complete cases files.
Age: 18-65

Right-handed

Races: all ethnic groups

Gender: male and female. Pregnant patients will be eliminated.

Patients must have normal or corrected-to-normal vision and hearing.

3.3. Study Hypothesis

Psychomotor symptoms are frequent in schizophrenia and MDD. Various brain regions may contribute to psychomotor slowing, but the precise pathophysiology remains unclear. Patients will be randomly assigned to four groups receiving sessions of TMS in different configurations. After TMS sessions, patients are expected to display an improvement of fine and gross motor activity as well as gesture performance. Across diagnoses, patients with motor retardation will benefit from inhibitory stimulation over SMA. Furthermore, TMS of various stimulation parameters is expected to affect disorder specific symptoms e.g. depressive symptoms and negative symptoms, which will be rated before and after TMS.

4. Study design

4.1. Targeted primary end point and secondary end points (effectiveness and safety parameters)

Main objective is the effect of TMS on psychomotor retardation (PR) in patients with major depressive disorder or schizophrenia. Primary outcome marker will be the change in psychomotor performance as assessed by Salpêtrière Retardation Rating Scales (SRRS). Clinical response will be defined as a 30% reduction of the SRRS baseline scores.
Secondary targets will be the effect of TMS on other motor parameters and on specific symptoms e.g. depressive or negative symptoms.
Efficacy parameters: TMS parameters may be of critical role determining the effect of the applied TMS on motor symptoms.
Safety parameters: As specific safety factors in relation to TMS, patients with 1. past history of epilepsy, or 2. other increased neuronal activity in Electroencephalography (EEG), 3. MRI contraindications and 4. substance misuse will be excluded. EEG recordings will be held for all patients before the beginning of TMS. Patients will be screened every 5 sessions with SRRS and actigraphy. In case of moderate deterioration of motor performance (30% change of initial ratings of SRRS or/and actigraphy) or adverse reactions during the TMS protocol, patients will be excluded from further participation in the study. .

4.2. Specification of the parameter that is of primary interest and other parameters that will be assessed as additional, secondary end points.

Primary outcome of the study will be efficacy as defined by >30% improvement from the baseline score of the Salpêtrière Retardation Rating Scales (SRRS). Outcome will be further evaluated as improvement in gross motor behavior (actigraphy), fine motor function (finger tapping test), and hand gesture performance (TULIA). In addition, we will investigate the effect of TMS on the disorder specific symptoms. Patients will be assessed with the Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960), Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) Beck Depression Inventory (BDI) (Beck et al., 1961), Positive and Negative Syndrome Scales (PANSS) (Kay et al., 1987) and Scales for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013) and Bush Francis Catatonia Rating Scales (Bush et al.,1996). Clinical ratings will be assessed at baseline and after the last TMS session by a rater blinded to stimulation protocol. Statistical analysis will comprise ANOVAs of motor variables and stimulation mode as between subject variable. Clinical response will be defined as a 30% reduction of the SRRS scores. Frequency of response will be compared between groups using Chi^2-Tests.

4.3 Study design, tabular overview, course of the study, study duration (for each participant), break-off criteria and procedure for unblinding

Study Design
Single site four arm randomized, sham-controlled trial to disentangle the pathophysiology of psychomotor retardation. We will investigate 80 in- and outpatients, aged between 18 and 65, diagnosed with MDD or schizophrenia,

displaying reduced levels of motor activity. Diagnoses will be given through application of MINI and review of the complete cases files. Only patients displaying reduced levels of motor activity assessed with Bern Psychopathology Scales (BPS) will be included and will be randomly assigned to four equal groups. Patients will be informed about the stimulation procedure and the goals of the study. Written informed consent will be obtained. Female patients will take a urine pregnancy test before the beginning of the TMS sessions and they will be required to use contraceptive methods during the TMS protocol in order to enroll in the study. In case of a suspicion of a pregnancy during the study despite the use of contraceptives a urine test will be taken. Subjects will undergo a series of diagnostic tests assessing primarily different psychomotor domains and secondarily disorder specific symptoms. Questions concerning demographic data (age, gender, education, occupational status) as well as substance use and medication will also be included. Each group will receive sessions of TMS of different stimulation parameters. Regardless of the type and the frequency of TMS, the stimulation protocol will consist of 15 daily sessions during a 3 week period. The four different stimulation conditions have been described above. Subjects will be reassessed after TMS.

Following assessments will be performed:

- Mini-International Neuropsychiatric Interview (MINI) – A validated structured diagnostic psychiatric interview.
- Bern Psychopathology Scales (BPS) – A validated quantitative and qualitative scales for the assessment of system-specific psychotic symptoms
- Actigraphy – gross motor activity levels will be recorded by wrist actigraphs
- Salpêtrière Retardation Rating Scales (SRRS) – A validated scales allowing the assessment various domains of psychomotor performance including gait, gross and facial motorics, speech and cognitive elements
- Finger tapping test – video-taped assessments of fine motor performance
- Test of Upper Limp Apraxia (TULIA) –video-taped, blinded ratings of gesture performance
- Patients with Major Depressive Disorder (MDD): Hamilton Rating Scale for Depression (HAMD), Montgomery Åsberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI) (Beck et al., 1961),
- Patients with Schizophrenia: Positive and Negative Syndrome Scales (PANSS), Scales for the Assessment of Negative Symptoms (SANS), Clinical Assessment Interview for Negative Symptoms (CAINS) and Bush Francis Catatonia Rating Scales (Bush et al.,1996).

Transcranial Magnetic Stimulation sessions

The first group will receive 15 Hz TMS over dorsolateral prefrontal cortex (DLPFC) repetitive TMS. As mentioned above, there is a considerable number of previous high frequency TMS trials at this site with significant effects on the psychomotor performance (Huber et al., 2003; Hausmann et al., 2004; Martis et al., 2003; Baeken et al., 2010). The rTMS protocol that will be used derives from the study of

Hernández-Ribas et al. (2013), which detected a significant antidepressant effect of high frequency TMS over DLPFC.

The second group will be tested with transcranial magnetic stimulation of 1 Hz rTMS over SMA/ pre- SMA. Low frequency TMS has been demonstrated to decrease motor cortex excitability, the motor consequences of which are still to be unraveled. Moreover, low frequency rTMS has shown a highly beneficial effect on motor symptoms in patients with Parkinson Disease (PD) (Shirota et al., 2013). We will use the stimulation protocol of the study of Shirota et al. (2013).

The third group will receive intermittent Thetaburst Stimulation (iTBS) 50 Hz over Supplementary Motor Area (SMA)/ Presupplementary Motor Area (pre-)SMA. iTBS is a modality of stimulation eliciting an excitatory effect on cortical excitability, applied primarily in patients with multiple sclerosis or post-stroke implications with beneficial findings. The findings of studies assessing the effect of iTBS over SMA on psychomotor performance in healthy individuals and patients with Parkinson Disease have been encouraging (Dusek et al., 2011; Ilic et al., 2012). We will apply the widely used protocol of the study of Huang et al. (2005).

The fourth group (control group) will receive sham stimulation over occipital cortex. In this group a placebo coil, similar to the real one will be used. According to the review of Loo et al. (2000) sham conditions including various coil positions have displayed a significant effect in many cases. Based on these findings, we chose to use a placebo coil over a different stimulation area expecting a negligible stimulation effect.
The complete stimulation details are given in section TMS Protocol. Regardless of the type and the frequency of TMS, the stimulation protocol will consist of 15 daily sessions during a 3 week period. The ratings mentioned above will be repeated after the end of the TMS.

Tabular overview

Selection of participants	Information about the procedure and the goals of the study
	Written informed consent is obtained
	Specific safety parameters for TMS sessions will be assessed
	EEG Recordings
	Bern Psychopathology Scales (BPS) for the assessment of motor activity levels
	Mini-International Neuropsychiatric Interview (MINI)
Assessment before TMS	Actigraphy
	Salpêtrière Retardation Rating Scales (SRRS)
	Finger tapping test
	Test of Upper Limp Apraxia (TULIA)
Specific assessment: patients with Major Depressive Disorder	Hamilton Rating Scale for Depression (HAMD)

	Montgomery Åsberg Depression Rating Scale (MADRS)
	Beck Depression Inventory (BDI)
Specific assessment: patients with schizophrenia	Positive and Negative Syndrome Scales (PANSS)
	Scales for the Assessment of Negative Symptoms (SANS)
	Clinical Assessment Interview for Negative Symptoms (CAINS)
	Bush Francis Catatonia Rating Scales (BFCRS)
Transcranial magnetic stimulation	Randomized allocation to four equal groups
	15 daily sessions (3 week period)
Assessment after TMS	Repetition of the assessments taken place before TMS

Course of the study

The study will be started immediately after ethical approval. Subject recruitment, testing and data analysis will last approximately 36 months.

The study will encompass the following periods:

Preparation (2 months)

At this period, the rater will be trained using the rating scales and the assessment methods. Additionally, the various departments of the clinic will receive detailed information on the study, while the function of all technical equipment and its' response to the design of the study will be tested. Modifications, if necessary, will be made.

Subject recruitment, ratings, TMS sessions and repetition of ratings (24 months)

During this phase, patients will be motivated to participate in the study. As the recruitment and screening of individuals will be taking place, TMS will be performed continuously during this period. Patients will be reassessed after every 5 sessions and in the end of the TMS. Contemporaneously, the data of the rating scales and methods will be digitalised and prepared for statistical analyses.

Analyses and publication (10 months)

After collecting all data, the final analyses will follow and manuscripts will be written.

Settings

Recruitment, screening and selection of patients will take place at the University Hospital of Psychiatry in Bern. The assessments and the TMS sessions will be carried

out at the Lab of the Department of Psychiatric Neurophysiology, University Hospital of Psychiatry in Bern.

Study duration for each participant

In total the duration for each participant will be as following

Duration of assessments

A) Pre TMS clinical ratings & tests 210 min
B) TMS sessions 30 min x 15 sessions=450 min
C) Post- TMS clinical ratings & tests 210 min

Procedure of unblinding

Reassessments after TMS sessions will be carried out by a rater, blinded to the stimulation allocation. The data of patients such as the TMS configuration delivered will be concealed in a sealed and opaque envelope and kept by the main investigator. The envelope will be opened only in case of adverse reactions, leading to discontinuation of the rTMS sessions and exclusion from the study.

4.4. Measures to minimize bias risk

After recruitment patients will be randomly allocated to four groups. Groups will be matched for age, gender, education and diagnose. Rater is blinded, patient is semi-blinded (has no knowledge of TMS, but could however find out where stimulation occurs).

5. Selection of the participants

5.1. Subject Recruitment

Patients with schizophrenia or major depressive disorder (MDD) according to DSM-5 criteria, displaying reduced levels of motor activity, will be recruited from the inpatient and outpatient departments of the University Hospital of Psychiatry in Bern.

5.2. Inclusion criteria

Right handed patients with MDD or schizophrenia according to DSM 5, ages 18-65 years old displaying reduced motor activity screened with the Bern Psychopathology Scale (BPS) (Strik et al., 2010). BPS is a validated, quantitative and qualitative scales for the assessment of system-specific psychotic symptoms. Diagnoses will be given through application of MINI and review of complete cases records. Patients must have normal or corrected-to-normal vision and hearing.

5.3. Exclusion criteria

History of head trauma

Substance misuse other than nicotine.

Pregnancy. Female patients will take a urine pregnancy test before the beginning of the TMS sessions and they will be required to use contraceptive methods during the study in order to enroll in the study. In case of a suspicion of a pregnancy during the study despite the use of contraceptives a urine test will be taken.

TMS specific criteria (exclusion criteria)

Past history of epilepsy

Other increased neuronal activity in Electroencephalography (EEG). EEGs of all patients will be recorded before the beginning of TMS. Patients displaying abnormal EEG findings will be excluded.

MRI contraindications, since such an examination maybe necessary in case of adverse reactions.

6. Assessment of effectiveness

6.1. Effectiveness parameters: measuring methods and reference dates

The efficacy of TMS sessions will be evaluated primarily as improvement in SRRS baseline score after treament. Furthermore, we investigate the effect of TMS on gross motor behavior (SRRS, actigraphy), fine motor function (finger tapping test), and hand gesture performance (TULIA). To this purpose, clinical ratings will be assessed twice, at baseline and after the last TMS session. Furthermore, changes may be demonstrated by the scales assessing the disorder specific symptoms; in patients with major depressive disorder, HAMD, MADRS and BDI, in patients with schizophrenia PANSS, SANS, CAINS and the Bush Francis Catatonia Rating Scales. Statistical analysis will comprise repeated measures ANOVAs of motor variables and stimulation mode as between subject variable. Clinical response will be defined as a 30% reduction of the SRRS scores.

7. Assessment of safety

7.1. Safety parameters: measuring methods and times

Specific safety parameters for TMS include: past history of epilepsy, pregnancy, other increased neuronal activity in Electroencephalography (EEG), MRI contraindications and substance misuse other than nicotine. Female patients will take a urine pregnancy test before the beginning of the TMS sessions and they will be required to use contraceptive methods during the study in order to enroll in the study. In case of a suspicion of a pregnancy during the study despite the use of contraceptives a urine test will be taken. These parameters will be observed and are explicit exclusion criteria. EEGs of all patients will be recorded before the beginning of TMS. Patients displaying abnormal EEG findings will be excluded. The rest of above mentioned parameters will be as well observed and are explicit exclusion criteria. After every 5 sessions, assessments of gross motor behaviour (SRRS,

actigraphy) will be repeated. In case of moderate deterioration of motor performance (30% change of initial ratings) patients will be excluded from the study.

7.2. Guarantee of follow-up examination of patients in case of adverse reactions.

The study will be carried out according to the protocol. In case of serious adverse events, which may be connected to the TMS stimulation or any relevant assessments (Art.42, KlinV), the Ethics Committee will be as soon as possible informed by the sponsor. Serious adverse events may include seizures or exacerbation of psychiatric symptoms. In such cases the TMS sessions will be immediately stopped and the patient will excluded from the study. A MRI examination will be held and any necessary additional medical consultations will be arranged.

8. Statistics

8.1. Definition of the primary end point and secondary end points

Primary outcome of the study will be clinical response as defined by >30% improvement from the baseline score of the Salpêtrière Retardation Rating Scales (SRRS). Moreover, gross motor behavior (actigraphy), fine motor function (finger tapping test), and hand gesture performance (TULIA) will be assessed at baseline and after the last TMS. Furthermore, we will investigate the efficacy of TMS on disorder specific symptoms; in patients with major depressive disorder, HAMD, MADRS and BDI, in patients with schizophrenia PANSS, SANS, CAINS and the Bush Francis Catatonia Rating Scales will be carried out before and after TMS. Statistical analysis will comprise ANOVAs of motor variables and stimulation mode as between subject variable. Clinical response will be defined as a 30% reduction of the SRRS scores. Frequency of response will be compared between groups using Chi^2-Tests.

8.2. Planned number of trial subjects with clearly stated justification (power analysis)

When we simulate a distribution of responders, in which two groups get 25% of the responders, the more effective group third group gets 40% and the most ineffective group only 10%, and compare this distribution to an equal distribution of 25% in each group, then the df is 3, noncentrality $\lambda = 14.22$, critical $X = 7.8$ and the effect size $\omega = 0.42$. Thus, we could expect a medium to large effect.

Applying a Chi^2-Test with this effect size of $\omega = 0.42$, a significance level of $\alpha = 0.05$, a power of $1-\beta = 0.90$ and a df = 3, then the total required sample size would be 79 subjects. Therefore, each group has to contain at least 20 subjects.

8.3. Description of the statistical methods foreseen and the planned intermediate assessments

Descriptive data analyses will be performed using Statistical Package for Social Sciences SPSS 17.0® (SPSS Inc., Chicago, IL, USA). In order to compare efficacy of the intervention arms, the primary outcome will be the frequency of patients

achieving response to psychomotor retardation (i.e. >30% improvement from SRRS baseline scores). This group statistic will be calculated using Chi^2-Tests.
In order to investigate the effect of rTMS on the psychomotor performance of participants, we will analyze changes in motor variables within and between groups using repeated measures-ANOVAs. This way, we will test for time effects and effects of stimulation protocol. In case of unequal distribution of descriptive parameters between groups, these parameters will be entered as covariates to the repeated measures ANCOVA. Before performing ANOVAs, a normalizing transformation will be carried out if necessary.
The same procedure will be followed in case of the diagnose specific symptoms ratings (BDI, MADRS, Hamilton, PANSS, SANS, CAINS).

To control if a possible improvement of psychomotor performance after rTMS may be attributed to a general clinical response, we will use the analysis of covariance (ANCOVA) with psychomotor performance ratings (before and after TMS) as within subjects factor and changes in ratings of diagnose specific symptoms ratings as covariate.

At three major recruitment steps (25% of total sample, 50% and 75% respectively) we will calculate the primary analysis. If one group proves to have significantly poorer outcome than the others, we will stop this study arm.

8.4. Planned significance level

Planned level of significance will be held as $p<0.05$.

8.5. Handling of missing data, dropout cases

Only complete data records with assessments at two time points will be entered in the analyses. In case of dropout we will perform an intention-to treat (ITT) analysis applying the last-observation-carried-forward method (LOCF). In case of revocation of patients (KlinV, Art.9), data will be anonymized.

9. Study-specific safety precautions and responsibilities

9.1. Safety precautions

The specific risks for TMS include past history of epilepsy, pregnancy, other increased neuronal activity in Electroencephalography (EEG), MRI contraindications and substance misuse other than nicotine. EEGs of all patients will be recorded before the beginning of TMS. Patients displaying abnormal EEG findings will be excluded. Female patients will take a urine pregnancy test before the beginning of the TMS sessions and they will be required to use contraceptive methods during the study in order to enroll in the study. In case of a suspicion of a pregnancy during the study despite the use of contraceptives a urine test will be taken. The rest of above mentioned parameters will be as well observed and are explicit exclusion criteria.

After every 5 sessions, assessments of gross motor behaviour (SRRS, actigraphy) will be repeated. In case of moderate deterioration of motor performance (30% change of initial ratings) during the study, patients will be excluded from the TMS. The investigators are responsible for the observation of the above mentioned criteria and the screening of patients. Patients will have to provide written informed consent, which will include explicit questions referring to the exclusion criteria. The safety criteria will be asked again before the beginning of TMS sessions and participants will have to warrant that none of the exclusion criteria is fulfilled.

9.2. If appropriate: exit examination in case of dropout

At the end of every week of the TMS stimulation, assessments of gross motor behaviour (SRRS, actigraphy) will be repeated. In case of moderate deterioration of motor performance (30% change of initial ratings), patients will be excluded from the study. In case of seizures or persisting headaches a Magnetic Resonance Imaging Examination will be held for diagnostic purposes.

10. Duties of the investigator

10.1. Confirmation that the conduct of the study will be in accordance with the GCP protocol, the current legal regulations and rights.

Hereby investigators confirm that they have knowledge of the GCP protocol, according to which the study will be carried out. All current legal regulations and rights will be additionally taken into account.

10.2. Adverse reactions, protocol changes, other changes, progress report and final report

Serious adverse events (SAE) may include seizures or exacerbation of psychiatric symptoms, which may be connected to the TMS or any relevant assessments (Art.42, KlinV). In such cases the TMS sessions will be immediately stopped and the patient will excluded from the study. Hereby the investigators guarantee that in case of any adverse events, as well as protocol changes or other changes, the Ethics Committee will receive a progress report and final report. Additionally, investigators confirm the knowledge of the AKEK safety reporting procedures (Arbeitsgemeinschaft der Schweizerischen Forschungs- Ethikkomissionen für klinische Versuche).

10.3. Statement of arrangements to cover damages

An insurance policy will be taken out and insurance form according to the requirements of the “schweizerische Ethikkomission” (“Versicherungszertifikat zu Handen der schweizerischen Ethikkomissionen”) is appended in order to assure that any possible damage will be covered.

11. Ethical considerations

11.1. Potential risks/ benefits balance

Clinical ratings & questionnaires:

The clinical tests and the questionnaires are non-invasive methods, used mainly in route examinations with no reported side effects.

TMS sessions:

TMS is a well known, clinical, diagnostic and therapeutic, non-invasive tool, widely used with seldom reported adverse reactions, as supported by an extensive body of studies and meta-analyses (Padberg & George, 2009). In rare single cases, seizures and mild headaches have been reported, while in very few cases negative effects on cognition, mood and various hormone levels were elicited (Wasserman, 1998; Burt et al., 2002). The TMS-induced seizures were in most cases self-limiting, and did not seem to have permanent squeal. Once again, it is important to point out that the risk of adverse reactions is noticeably low, below 1/1000 investigations (Information Brochure on rTMS, rTMS committee of the International Federation of Clinical Neurophysiology). TMS parameters (intensity, frequency, number of stimulations) of the presented study will be in accordance to international safety guidelines (e.g. Wasserman , 1998).

TMS potential adverse effects will be minimized and the risk/benefit ratio will be supportable by following the TMS safety parameters, as they were above described. Any severe adverse effect will lead to discontinuation of the rTMS protocol in the respective patient. TMS exclusion criteria are past history of epilepsy, other increased neuronal activity in Electroencephalography (EEG), MRI contraindications and substance misuse. EEG recordings of all patients will be conducted before the beginning of rTMS sessions.

11.2. Benefits for the participants

Patients with motor abnormalities are expected to display an improvement of motor performance after receiving different configurations of TMS. A potential beneficial effect of TMS on the disorder specific symptoms may be also detected. Additional benefit will be the gained knowledge, possibly helpful for future patients with the same problems.

Importance of the trial

Psychomotor retardation appears to be of central significance across a spectrum of mental disorders such as schizophrenia and depression subtypes, in which the planning and the execution of movements is affected, resulting in disturbances in main psychomotor domains (Morrens et al., 2007; Schrijvers et al., 2008). The occurrence of PR is strongly associated with poorer quality of life (Muslimovic et al., 2008) and it may have a restraining effect on common physical activities of patients (Putzhammer et al., 2005; Schrijvers et al., 2008). Our study of the efficacy of different TMS protocols on PR will significantly extend the knowledge on the pathophysiology of PR. Moreover, the study will inform on potential mechanisms for noninvasive therapeutic brain stimulation to target psychomotor retardation.

12. Quality control and quality assurance: description of measures

The study conforms to the declaration of Helsinki. Participants will provide written informed consent and will be informed about the option to drop out of the study at any moment.

12.1. Warranty to access to original data, permission of audits and monitoring by authorities, Ethic Committee and quality control

Direct access to original data and inspection by pertinent authorities and Ethic committee will be provided if required.

12.2. Handling of data and samples, archiving and destruction

The data will be encoded (subjects' initials and date of birth will be used to code their data), digitalised and processed exclusively on the local computer of the principal investigator, while a copy of them will be kept on server of the Department of Psychiatric Neurophysiology, University Hospital of Psychiatry in Bern, following the strict security rules of the Department. Only the principal investigator will be aware of the decoded data, while the other investigators will use the encoded data. The encryption key as well as the list of the participants will be kept by the main investigator. The encryption code and the list guarantee the traceability of the patients' data (KlinV, Art.18). In case of revocation (KlinV, Art.9), data will be anonymized. Paper records will be archived in the archive of the University Hospital of Psychiatry in Bern for 10 years and they will be destructed according to the security rules of the archive. Digital data will be as well preserved for 10 years and afterwards will be deleted. In the meantime they may be used in upcoming studies. No genetic examinations/transfers of samples are planned.

12.3. Data collected specifically for the study

Pre- and post-TMS assessments and tests will be registered. No data will be included in the patient files.

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