Preliminary study on the Effect of repetitive Trans-cranial Magnetic Stimulation on Negative Symptoms in Patients with schizophrenia

Thesis

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List of Abbreviations

Abb.	Full term
ACEiii	Addenbrooke Cognitive Examination
ALKS 3831	Alkermes
ASUIP	Ain Shams University Hospitals
BCL9	B-cell CLL/ lymphoma9
BDNF	Brain derived neurotropic factor
BDNF	Brain-derived neurotrophic factor
C9orf5	Chromosome9openreading frame5
CBT	Cognitive behavioral therapy
COMT	Catechol-O-methyltransferase
CTNNA3	Catenin (cadherin-associated protein), alpha3
DLPFC	dorsolateral prefrontal cortex
DRD2	Dopamine receptor D2
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive therapy
ERP	Event Related Potentials
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
ICD	International Classification of Diseases
IQR	Interquartile range
Lu AF35700	Lundbeck
MEP	Motor evoked potential
mGlu2/3	Metabotropic glutamate 2/3
MIN-101	Minerva Neurosciences
MMN	Mismatch negativity
NMDA	N-methyl-D-aspartate receptors
NRG1	Neuregulin-1

List of Abbreviations Cont...

Abb.	Full term
OCD	Obsessive-Compulsive Disorder
PANNS	Positive and Negative Syndrome Scale
PANSS	Positive and Negative Score Scale
PANSS	Positive and Negative Syndrome Scale for Schizophrenia
PET	Positron Emission Topography
PTSD	Posttraumatic Stress Disorder
RCT	Randomized Control Trials
RNF144	Ring finger protein144
rTMS	Repetitive Trans-cranial Magnetic Stimulation
SANS	Scale for the Assessment of Negative Symptoms
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorder
SST	Social skill training sessions
ST3GAL	1ST3beta-galactosidealpha-2,3-sialyltransferase 1
SWS	Slow wave sleep
TDC	Trans Cranial Direct Current stimulation
TMS	Trans magnetic stimulation
WCST	Wisconsin Card Sorting Test
WHOQOL-BREF	World Health organization Quality of life – BREF
ZNF385D	Zinc finger protein 385D

Introduction

Schizophrenia is a complex chronic disorder with 1 percent of incidence in general population, the disease has three major symptoms, these include positive symptoms such as delusion, hallucination, disorganized thinking and speech, negative symptoms such as anhedonia and withdrawal from social life as well as cognitive disorders such as reversal of learning, and memory ***(Canan et al., 2017).***

Negative symptoms have been demonstrated to be the most relevant predictor of increased future socio-occupational dysfunction and poorer quality of life ***(Chue & Lalonde, 2014).***

Impaired functioning of the prefrontal cortex, mainly reduced activation of the dorsolateral prefrontal cortex, has consistently been reported in patients with schizophrenia ***(Glahn et al., 2005).*** Furthermore, there are growing evidences for a correlation between severity of negative symptoms and hypo functioning of the left dorsolateral prefrontal cortex ***(Gonul et al., 2003).***

Repetitive Trans-cranial Magnetic Stimulation (rTMS) is a relatively safe and non-invasive tool to modulate neuronal activity; rTMS uses alternating magnetic fields in a certain frequency to induce an electric current in the underlying brain tissue. High-frequency rTMS has been shown to increase local

cortical excitability and low-frequency rTMS has been shown to decrease excitability ***(Fitzgerald et al., 2006).***

Administering high frequency rTMS to the left dorsolateral prefrontal cortex might possibly increase brain activity in the stimulated area and to change brain activity in associated regions that are part of the same neural circuit ***(Strafella et al., 2001).***

Possibly, rTMS may provoke neural plasticity in the prefrontal circuits of the brain by facilitating dopaminergic, GABAergic and/or glutaminergic neurotransmission and which may be reflected by a change in brain activation after rTMS sessions treatment ***(Luborzewski et al., 2007).***

Therefore, there might be improvement of negative symptoms in patients with schizophrenia after receiving rTMS combined to pharmacotherapy.

Aim of the Work

Assessment of the effect of rTMS on negative and cognitive symptoms in schizophrenic patients after receiving active stimulation combined to pharmacotherapy compared to pharmacotherapy alone.

Chapter 1

Schizophrenia

Schizophrenia is a devastating lifelong psychiatric syndrome characterized by impairment in the reality testing. It generally presents with three major symptom clusters, positive symptoms such as delusions, hallucinations, negative symptoms consisting of social withdrawal, avolition, inattentiveness to interpersonal cues, and cognitive impairments including deficits inattention, executive functioning and working memory ***(Evangelia et al., 2015).***

The life time prevalence of schizophrenia has generally been estimated to be about 1 percent worldwide. Males have a more severe illness with earlier onset with prevalence approximately 1.4 times higher than females. The Age of onset of schizophrenia symptoms is the early 20s for males and the late 20s for females ***(Arnaldo & Ferris, 2018).***

Nowadays as we are moving to biological approach in psychiatry, still the diagnosis of schizophrenia is difficult because there is no single symptom which is unique to schizophrenia and there are no definitive blood tests or brain imaging for the disorder. Making a diagnosis currently requires recognizing a constellation of symptoms to be matched with the diagnostic criteria of the International Classification of Diseases (ICD) system or Diagnostic and Statistical Manual of Mental Disorders (DSM) system, seeing a deterioration in the

level of functioning of the person with the symptoms, and ruling out other possible explanations for the observed disturbance ***(Getinet, 2016).***

Negative symptoms of Schizophrenia

Negative symptoms have long been neglected with respect to diagnosis and therapeutic treatment of schizophrenia. In contrast to positive symptoms, negative symptoms have been defined as a reduction of normal functions either to motivation and interest, such as avolition, anhedonia, and asociality, or to expressive functions such as blunted affect and alogia ***(Silvana et al., 2018).***

Negative symptoms of schizophrenia include: Blunted affect which is defined as decrease in the expression of emotion and reactivity to events as observed during the spontaneous or elicited expression of emotion. Alogia which is defined as reduction in quantity of words spoken and in spontaneous elaboration. A sociality which is defined as reduced social interactions and initiative due to decreased motivation for and interest in forming and maintaining relationships with others. Anhedonia which is defined as reduced experience of pleasure for a variety of activities. Avolition which is defined as reduced initiation and persistence of goal-directed activity due to reduced motivation ***(Ahmed et al., 2015).***

Many Studies across different countries and clinical records show that more than a third of patients with schizophrenia suffer from poor motivation and blunted affect, While the assessment of the domain of negative symptoms has improved considerably; the understanding of the underlying pathophysiological mechanisms still remains limited ***(Patel et al., 2015).***

Negative symptoms usually present prior to the onset of frank psychosis defining schizophrenia and are frequently observed in prodromal cases and individuals with schizophrenia spectrum personality disorders, the presence of these symptoms at these phases is important because functional decline occurs early in the course of the disorder and overall outcome has been observed to be directly correlated with functional ability prior to onset of psychosis ***(Strassnig et al., 2018).***

Negative symptoms can be either primary or secondary, the deficit syndrome is a subgroup of patients with schizophrenia who have primary or idiopathic and enduring negative symptoms that are not secondary to other aspects of the disorder, such as psychosis, depression or medication effects. While secondary could be due to positive, affective, or extrapyramidal symptoms, antipsychotic-induced sedation, environmental deprivation, and other disorder-related and treatment-related factors ***(Kirkpatrick et al., 2017).***

Differentiation of primary(Deficient) and secondary negative symptoms has important treatment value since there is no effective treatments exist for primary negative or deficit symptoms. In contrast to primary negative symptoms, secondary negative symptoms might be responsive to the available treatments; for example, negative symptoms secondary to positive symptoms might be responsive to effective antipsychotic treatment, whereas negative symptoms secondary to depression might be responsive to antidepressant treatment ***(Kirschner et al., 2017).***

Unfortunately, secondary negative symptoms might not be responsive to treatment of their underlying cause. A large number of patients with schizophrenia who has primary or secondary negative symptoms, usually acquire changes over the course of the disorder. The attempt to identify patients with enduring primary or secondary negative symptoms changes has led to additional type of negative symptoms, called schizophrenic patients with disabling negative symptoms, which is markedly larger than the patients with either primary or secondary negative symptoms ***(Galderisi et al., 2017).***

Patients with prominent negative symptoms of schizophrenia usually have poor premorbid functional level even since early development. It is believed that those patients have poorer premorbid level of function in comparison with patients with prominent positive symptoms, Also several studies showed