Towards neurophysiological biomarkers to assess repetitive transcranial magnetic stimulation treatment for patients with schizophrenia and auditory verbal hallucinations

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Doctor of Philosophy

January 2022

Department of Engineering

Reykjavík University

Ph.D. Dissertation

Towards neurophysiological biomarkers to assess RTMS treatment for patients with schizophrenia and auditory verbal hallucinations

Dissertation of 30 ECTS credits submitted to the
Department of Engineering
at Reykjavík University in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy (Ph.D.) in Clinical Neurophysiology
January 2022

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ISBN 978-9935-9620-2-7 electronic version
ISBN 978-9935-9620-3-4 print version

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Towards neurophysiological biomarkers to assess repetitive transcranial magnetic stimulation treatment for patients with schizophrenia and auditory verbal hallucinations

Ovidiu C. Banea, January 2022

Abstract

Background: Repetitive transcranial magnetic stimulation (RTMS) has been suggested as a possible therapeutic alternative for patients with schizophrenia (SCZ) and treatment-resistant auditory verbal hallucinations (AVH). The aim of the studies presented here was to investigate how RTMS affects clinical symptoms, electroencephalographic responses, and brain functional networks. We suspected improvement of symptoms accompanied by changes in EEG activity, event-related potentials, and sensory gating.

Subjects and methods: Ten patients with schizophrenia (mean age 32.4, SD = 6.85, 7m, 3f) and six healthy controls (mean age 30.3, SD = 7.5, 4m, 2f) participated in this study. Nine patients were on antipsychotic medication. The patients were randomly selected into two groups, the treatment group (TG) and the control group (CG). The active low-frequency 1Hz RTMS was delivered in ten daily sessions of 900 pulses at two different EEG locations: T3-P3 (TG) and Cz (CG). Clinical symptoms were investigated with psychometric scales like Quality of Life (QoL), Depression Anxiety Stress Scales (DASS), and Psychotic Symptom Rating Scale with Auditory Hallucinations Subscale (PSYRATS AHS). The neurophysiological tests employed were cortical and cutaneous silent period, mid-latency auditory evoked potentials (P50, N100, P200) using a paired click paradigm, P300 obtained with an auditory oddball paradigm, and the cognitively driven auditory-motor task (AMT). Time, frequency domains, and functional network organization of different neurophysiological markers were analyzed. P300 oscillatory activity was analyzed with EEG source connectivity (e.g., participation coefficient) and for the auditory-motor task-induced oscillations, we used network integration parameters of graph theory (i.e., characteristic path length - CPL and small worldness - SW). The patient's results obtained after the treatment (T2) were compared with data obtained at baseline condition (T1) and with data from the third group of healthy controls (HC).

Results: There were no significant changes between TG and CG on QoL, DASS, and PSYRATS AHS scores or neurophysiological data after the RTMS treatment. We also calculated pre-post RTMS changes for all patients. N100 showed the most marked changes after RTMS in left temporoparietal region, from -0.57 μV (SD 0.97) to -2.39 μV (SD 1.59), ($p = 0.006$, $\eta2 = 0.346$) and in medial posterior region ($p = 0.038$, $\eta2 = 0.218$) suggesting a modulation of this marker over both stimulation sites. After RTMS, N100-P300 voltage increased for six patients, two in TG and four in CG, but also decreased in patients from TG who showed the best clinical outcome. The EEG power spectral density (PSD) during the auditory oddball paradigm increased in T2, mainly for the alpha band and beta band globally, for six subjects, two in TG and four in CG. The connectivity results for the frequent stimuli of the auditory oddball paradigm showed increased network segregation during T2 for the beta band, in seven patients, four in CG, and three in TG. The study revealed that patients with schizophrenia exhibit higher gamma PSD in a period between two auditory commands

of AMT, compared to HC, which was modified by RTMS without being significant. The change was visible, locally, over the left temporoparietal region, when the task was done with the non-dominant hand, showing that during this condition, gamma synchronization is a marker of "neural effort" and workload during the working memory-related time and not during the auditory or motor cortical activation. Graph theory analyzed for low-gamma EEG activity elicited in between the auditory stimuli, an epoch of the auditory-motor task we called "non-cortical activation" and which is related to the working memory, showed a decreased SW index after RTMS when the task was performed with the non-dominant hand. This SW effect observed in the patients was similar to that of the HC group. Kendall's tau-b correlation showed a strong, negative correlation between the SW index of low-gamma phase oscillations and PSYRATS AHS scores in T1, which was statistically significant ($\tau b = -0.788$, $p = 0.032$). After RTMS (T2) the correlation was strongly positive ($\tau b = 0.733$, $p = 0.039$).

Discussion: The sample size of this study was small to achieve TG-CG statistical significance (e.g., PSYRATS AHS pre-calculated N was 16). Individual data showed controversial results, sometimes with the improvement of AVH severity and neurophysiological data in patients treated at the Cz EEG location. N100 from the paired click paradigm showed the most marked changes at the left temporoparietal region. P300 was performed with a passive auditory oddball paradigm by "automatic" discrimination between two tones without asking the subject to move the finger or count the target stimuli. The findings we obtained with P300 amplitude, which in most cases decreased after RTMS, might be in direct relation to a habituation effect, which is seen in healthy subjects (Polich, 1989).

Conclusion: Based on the patient´s clinical evaluations and all the neurophysiological measurements presented in the studies of this thesis we cannot affirm that left temporoparietal (T3-P3) RTMS is more effective than vertex (Cz) RTMS in patients with schizophrenia and auditory verbal hallucinations. Some interesting neurophysiological observations were made, particularly changes of N100 amplitude at the left temporoparietal region and low gamma activity during the period in between auditory commands of a cognitively driven task. N100 amplitude measured from a paired click paradigm and low gamma activity measured in-between auditory stimuli of AMT performed with the non-dominant hand might be of interest to assess the neuromodulatory aftereffects of RTMS in patients with SCZ and AVH. The small-world network of low gamma activity showed a significant main effect of the condition (AMT and resting state) for HC and SCZ-T2 suggesting that RTMS might have influenced the network by restoring the SW index. Further, studies with a multimodal neurophysiological approach are necessary to assess RTMS effectiveness for patients with SCZ and AVH.

Hver eru taugalífeðlisfræðigáhrif fyrir og eftir TMS meðferð hvað raflífeðlisfræðilegra breytur varða hjá sjúklingum með geðklofa og heyrnartals ofskynjanir?

Ovidiu C. Banea, januar 2022

Útdráttur

Bakgrunnur: Undanfarin ár hefur raðsegulörvun (RTMS) verið sífellt meira notuð sem meðferðarúrræði fyrir sjúklinga með geðklofa (SCZ) og meðferðarónæmar heyrnar- og talofskynjanir (AVH). Markmið rannsóknanna sem kynntar eru hér var að kanna hvernig RTMS hefur áhrif á klínísk einkenni, raflífeðlisfræðilega svörun og starfsemi heilans. Áætlað var að jákvæðar taugalífeðlisfræðilegar breytingar myndu sjást samfara bættum klínískum einkennum í kjölfar meðferðar.

Aðferðir: Tíu sjúklingar með geðklofa (meðalaldur 32,4, SD = 6,85, 7 kk, 3 kvk) og sex heilbrigðir einstaklingar (meðalaldur 30,3, SD = 7,5, 4 kk, 2 kvk) tóku þátt í þessari rannsókn. Níu af tíu sjúklingum voru á geðrofslyfjum. Sjúklingarnir voru valdir af handahófi í tvo hópa, meðferðarhóp (TG) og viðmiðunarhóp (CG). Hamlandi, lágtíðni (1Hz) RTMS var veitt í tíu daglegum lotum (900 púlsar í hvert skipti) á tveimur mismunandi heilaritasstöðum: T3-P3 (TG) og Cz (CG). Klínísk einkenni voru metin með eftirfarandi sálfræðilegum kvörðum: Quality of Life (QoL), Depression Anxiety Stress Scales (DASS), og Psychotic Symptom Rating Scale with Auditory Hallucinations Subscale (PSYRATS AHS). Taugalífeðlisfræðilegu prófin sem notuð voru könnuðu; 1) þögla tímabil heila og mænu, og 2) Heyrnar-hrifrit (early and mid-latency ERPs), þar sem svörun við pöruðum tónum (e. paired click paradigm) var könnuð (P50, N100, P200 bylgjurnar) annars vegar, og svörun á frávikstónaprófi (e. oddball-task) til að kanna P300 bylgjuna hins vegar. Auk þess var annað próf sem kannaði svörun eftir fyrirmælum (e. auditory-motor task, (AMT)). Tími, tíðnisvið og starfræn netkerfi voru greind. Uppsprettu tengingar heilaritsins (e. EEG source connectivity) voru metnar fyrir P300 bylgjuna (t.d. participation coefficient) og AMT var greint út frá graffræði (e. Graph theory), þar sem tengsl milli heilasvæða voru skoðuð (t.d. Characteristic path length (CPL) og small worldness (SW)). Niðurstöður sem fengust eftir meðferð (T2) voru bornar saman við niðurstöður sem fengust fyrir meðferð (T1) og gögnum frá þriðja hópi heilbrigðra einstaklinga (HC).

Niðurstöður: Engar marktækar breytingar sáust á milli TG og CG á QoL, DASS og PSYRATS AHS svörunar né taugalífeðlisfræðilegum mælingum eftir RTMS meðferðina. Einnig voru reiknaðar út breytingar á taugalífeðlisfræðilegum mælingum og spurningalistum fyrir og eftir RTMS fyrir alla sjúklinga sem einn hópur. Þar sýndi N100 mest áberandi breytingar eftir RTMS á mörkum vinstra gagnauga- og hvirfilblaðs, frá -0,57 µV (SD 0,97) í -2,39 µV (SD 1,59), ($p = 0.006$, $\eta2 = 0.346$) og á miðlægu hvirfilblaði ($p = 0.038$, $\eta2 = 0.218$) sem bendir til þess að heilastarfsemi hafi breyst nálægt báðum örvunarstöðum. Eftir RTMS jókst N100-P300 spenna hjá sex sjúklingum, tveimur í TG og fjórum í CG, en lækkaði einnig hjá sjúklingum úr TG sem sýndu bestu klínísku útkomuna. Heildar aflrófsþéttleiki (e. power spectral density, (PSD)) á meðan á frávikstónaprófi stóð jókst í T2, aðallega fyrir alfa-bandið og beta-bandið yfir allt höfuðið, hjá sex einstaklingum, tveimur í TG og fjórum í CG.

Niðurstöður netkerfa-tenginga (e. connectivity) fyrir tíð áreiti í frávikstónaprófinu sýndu aukinn aðskilnað við T2 athugun fyrir beta-bandið hjá sjö sjúklingum, fjórum í CG og þremur í TG. Rannsóknin leiddi í ljós að PSD svið hjá sjúklingum með geðklofa hækkaði í gamma-bandinu á tímabilinu milli tveggja hljóðskipana í AMT prófinu, samanborið við HC, sem var breytt án þess að vera marktækt. Breytingin var sýnileg og staðbundin yfir mörkum vinstra gagnauga- og hvirfilblaðs, þegar verkefnið var unnið með víkjandi hendi. Það bendir til þess að í þessu ástandi gæti gamma-samstilling verið merki um „taugaátak“eða vinnuálag þegar vinnsluminni er virkt, en ekki á meðan á heyrnar- eða hreyfibarkarvirkjun stendur. Graffræði var greind með tilliti til lág-gamma heilavirkni, á milli áreita í AMT verkefninu sem við kölluðum „non-cortical activation“, sem tengist vinnsluminni. Sú greining sýndi lækkuð SW gildi eftir RTMS þegar verkefnið var framkvæmt með víkjandi hendi. Þessi SW áhrif sem sáust hjá sjúklingunum voru svipuð og hjá HC hópnum. Tau-b fylgni Kendalls sýndi sterka, neikvæða fylgni á milli SW gilda lág-gamma fasa-sveiflna og PSYRATS AHS svörunar í T1, sem var tölfræðilega marktæk ($\tau b = -0{,}788$, $p = 0{,}032$). Eftir RTMS (T2) sást sterk jákvæð fylgni þar á milli ($\tau b = 0{,}733$, $p = 0{,}039$).

Umræða: Þátttakendur í þessari rannsókn voru of fáir til að ná fram marktækum mun á milli hópanna TG-CG (t.d. var hópastærð fyrir PSYRATS AHS fyrirfram reiknuð fyrir 16 einstaklinga). Niðurstöður á einstaklingsgrunni sýndu umdeildar niðurstöður, þar sem meðal annars klínísk einkenni og taugalífeðlisfræðileg svörun batnaði hjá sjúklingum sem voru meðhöndlaðir á Cz svæðinu. Í verkefni þar sem tónapör voru lögð fyrir þátttakendur, sýndi N100 bylgjan aðlögun á mörkum gagnauga- og hvirfilblaðs eftir meðferð. P300 bylgjan var einnig mæld, þar sem tveir mismunandi tónar heyrðust, og annar þeirra var sjaldgæfari en hinn. Verkefnið var “óvirkt” í þeim skilningi að það krafðist engrar virkrar svörunar. Niðurstöðurnar úr greiningu sveifluvíddar P300 sem í flestum tilfellum minnkaði eftir RTMS, gætu verið í beinu sambandi við vanaáhrif (e. habituation) sem sjást hjá heilbrigðum einstaklingum (Polich, 1989).

Ályktun: Niðurstöður rannsóknarinnar geta ekki með óyggjandi hætti sagt til um hvort RTMS sé áhrifarík meðferð fyrir sjúklinga með geðklofa og meðferðarþráar heyrnarofskynjanir. Þrátt fyrir það bar á áhugaverðum taugalífeðlisfræðilegar niðurstöðum. Ber þá helst að nefna breytingar á N100 sveifluvídd á mótum vinstra gagnauga- og hvirfilblaðs og lág-gammavirkni á tímabilinu á milli fyrirmæla í AMT. Áhugavert væri í framtíðinni að kanna frekar áhrif RTMS hjá þessum sjúklingahóp hvað varðar sveifluvídd N100 þar sem tóna-pör voru lögð fyrir (e. Paired click paradigm) og lág-gamma virkni mæld á milli fyrirmæla (AMT), framkvæmt með víkjandi hendi. Niðurstöður úr graffræði-greiningu sýndu að SW hvað varðar lág-gammavirkni sýndi marktæk meginhrif í tveimur verkefnum (AMT og í hvíld (e. resting state)) hjá heilbrigðum og hjá sjúklingum eftir meðferð (T2). Möguleg túlkun á því gæti verið að RTMS hafi áhrif á virkni netkerfa með því að færa SW virkni í átt að heilbrigðu ástandi. Þessi rannsókn sýnir að fjölþætt taugalífeðlisfræðileg nálgun getur veitt ítarlegar upplýsingar þegar meta á virkni RTMS meðferðar fyrir sjúklinga með geðklofa og heyrnarofskynjanir.

The undersigned hereby certify that they recommend to the Department of Engineering at Reykjavík University for acceptance this Dissertation entitled **Towards neurophysiological biomarkers to assess repetitive transcranial magnetic stimulation treatment for patients with schizophrenia and auditory verbal hallucinations** submitted by **Ovidiu Constantin Banea** in partial fulfillment of the requirements for the degree of **Doctor of Philosophy (Ph.D.) in Clinical Neurophysiology.**

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December 2, 2021

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Ovidiu Constantin Banea
Doctor of Philosophy

I dedicate this work to all the patients with psychiatric disorders, especially to those suffering from schizophrenia and auditory verbal hallucinations, and to their families.

Acknowledgments

I am very grateful to Dr. Paolo Gargiulo and Dr. Eric Wassermann, my doctoral thesis supervisors. Since our first meeting at Reykjavík University, Paolo helped me to understand the importance of team working and how to build a strategic roadmap and to persuade the original ideas in the field of biomedicine. During the last three-four years, Paolo knew how to motivate me through the consecutive works we followed to understand the brain neurological networks measured with dense array 256 channels EEG. In 2012 it was the first time I discovered Dr. Wassermann's activity in the field of TMS by consulting the scientific literature and direct mentions made by Dr. Josep Maria Espadaler Gamissans and Dr. Josep Valls-Solé, neurophysiologists with whom I discovered the secrets of TMS in Barcelona Spain. I met Eric for the first time in 2018 at the Behavioral Neurology Unit in Bethesda, Maryland U.S.A. when he received me at the National Institute of Neurological Disorders and Stroke (NINDS) during my visit to Washington D.C. for the 31st International Congress of Clinical Neurophysiology. A modest man who had the patience to listen and to provide all feedback to my ideas and concerns regarding the treatment with TMS and the neurophysiological assessment of the possible RTMS aftereffects on neuroplasticity.

I thank Dr. Elias Ólafsson, professor and chairman at the Department of Neurology, at the National University Hospital of Iceland, who created the possibility to perform the RTMS on the patients in our department. I remember the valuable advice he gave me before starting the doctoral program: “First, be sure you have established the methods chapter very well”.

Special thanks I want to address to my colleagues Eysteinn Ívarsson and Aron Dalin Jónasson for their help with TMS treatment and neurophysiological measurements. To Katrín Einarsdóttir and Basia Gancarek-Śliwińska who never hesitate to help with the schedule or work planning. However, it is equally important for me to recognize all my coworkers within the AVH TMS Icelandic project, for the help at Reykjavik University. Thank you, Valerio Gargiulo, Sara Marcu, Elena Pegolo, Romain Aubonnet, Fabio Barollo, Alec Shaw, Rún Friðriksdóttir, Aníta Ósk Georgsdóttir, Roberta Sirica and Sólveig Agnarsdóttir.

I thank Lucas Galdino Bandeira dos Santos for all the help with the graph theory and statistical analysis and to Timm Rosburg for all the patience, professionalism, and help with the technical aspects of our data regarding the N100 study. I thank Waldemar Karwowski and Yong He for the images describing graph theory properties and their interest in this work.

I am very grateful to Dr. Sigurjón B. Stefánsson, my senior colleague who encouraged the investigation of high-density EEG with Dr. Paolo Gargiulo and gave many words of advice. I thank Bjarni Guðmundsson, my colleague at the Neurophysiology Unit for his support, the lessons of the Icelandic language, and help with the work organization for our patients. Many thanks to neuropsychologist Viktor Jónasson who on the first trip we had on Esjan mountain with his brother and my colleague Aron he asked if we could treat patients with schizophrenia and auditory verbal hallucinations with TMS. With help of Brynja Björk Magnúsdóttir and Magnús Haraldsson, he informed Icelandic psychiatrists of the possible use of this novel treatment and the patients could be introduced to the study. Thank you all.

Finally, I would not have been where I am today without the help and understanding of my wife, my son, my brother, my parents, and all the large family and friends from Romania, Spain, and Iceland.

Preface

This dissertation is original work by the author, Ovidiu C. Banea.

I graduated as an environmental ecologist in 1997 and a medical doctor in 2000, in Sibiu Romania. In 2004, I moved to Spain where I worked as a primary care doctor and emergency medicine doctor before I finished Sports Medicine (2007) and Clinical Neurophysiology (2015) medical specialties. Right after, I started Clinical Neurophysiology in 2011 as MIR (*Médico Interno Residente*) at "del Mar Hospital" in Barcelona, I was interested in transcranial magnetic stimulation (TMS) and its clinical use in patients with psychiatric illness. With my senior consultant physician, Dr. Josep Maria Espadaler, and my colleagues Alba León Jorba, Cid Aurelio Delgado Pugley, and Alessandro Principe we worked with TMS in patients with Down Syndrome studying their intracortical brain dynamics using ICI-ICF paradigms. In 2012, I proposed a clinical study with repetitive transcranial magnetic stimulation treatment for patients with unipolar major depressive episodes within our laboratory, which unfortunately was not implemented. In the last ten years, I used TMS for many patients with brain tumors in preoperative studies to assess and map the eloquent speech and motor areas of the brain. I worked with TMS in patients with suspected amyotrophic lateral sclerosis, primary lateral sclerosis, myelopathic syndromes, spinal stenosis, and intramedullary tumors.

In June 2017, one year after my arrival to the National University Hospital of Iceland, with the help of neurologist Eric Wassermann, neurophysiologist, and psychiatrist Sigurjón B. Stefánsson and biomedical engineer Paolo Gargiulo I proposed a doctoral study[1] to the University of Reykjavik entitled "*Biological neural networks assessment with TMS-EMG and TEP in patients with brain tumors and symptomatic epilepsy*". TEPs or TMS-EEG evoked potentials provide a direct assessment of cortical excitability and long-range cortical connectivity. The study was motivated by the lack of preoperative navigation TMS in Iceland and its implementation was determined by the acquisition of a modern TMS device suitable to EEG online recordings. The difficulty of such an acquisition and the need for international collaboration to obtain enough patients let this proposal at a theoretical level.

Following this interest in analyzing brain biological neural networks, in 2018, I proposed the AVH-TMS Icelandic clinical trial[2]. This work was motivated by the recent studies with TMS therapy for patients with schizophrenia and auditory verbal hallucinations. Víktor D. Jónasson was the first neuropsychologist who was interested in this kind of treatment for Icelandic patients.

[1] The *critical view* was presented during the 27th Edition of ANT Neuromeeting in Beaune, Burgundy France https://www.ant-neuro.com/sites/default/files/files/Final_Program-ANT_Neuromeeting_2018.pdf

[2] AVH-TMS Icelandic clinical trial lasted three years, between 2018-2021 and was organized by Reykjavík University, Department of Biomedical Engineering, Clinical Neurophysiology Unit of Neurology Department, National University Hospital of Iceland, and Icelandic Psychiatric Hospital Kleppur

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List of Abbreviations

AVH	Auditory Verbal Hallucinations
SCZ	Schizophrenia
TMS	Transcranial Magnetic Stimulation
RTMS	Repetitive TMS
T3-P3	EEG location, left temporoparietal
Cz	EEG location "*Central zentrum*" or vertex
CSP	Cortical silent period
CuSP	Cutaneous silent period
ERP	Event-related potentials
MLAEP	Mid-latency auditory evoked potentials
N100	Negative wave at 100 ms
P300	Positive wave at 300 ms
DE	Delay epoch
MCA	Motor cortical activation
ACA	Auditory cortical activation
NCA	Non-cortical activation
GBA	Gamma Band Activity
SW	Small Worldness
CPL	Characteristic Path Length
PC	Participation Coefficient
AMT	Auditory-motor Task

List of Symbols

Symbol	Description	Value/Units
η^2	Eta-squared	
μV	Microvolt	

1 Chapter. Introduction

1.1 Schizophrenia

1.1.1 Epidemiology of schizophrenia

Schizophrenia is a chronic and severe mental disorder affecting 20 million people worldwide (Vos et al., 2017) with a median incidence of 15.2 cases per 100,000 persons. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5), the lifetime prevalence of schizophrenia is approximately 0.3%-0.7%. The peak age of onset of the first psychotic episode is in the early to mid-twenties for males and late twenties for females (Hurley, 2017).

In Iceland, patients with schizophrenia and other mental illnesses have been hospitalized since 1907 (Karlsson, 1988). The total population living in Iceland at 1st of January 2018 was 348,450 (*Population 1st of January 2018 - Statistics Iceland*, n.d.). We conducted a recent retrospective analysis carried out at the National University Hospital of Iceland for the 2012-2018 period, by searching the medical records for F20 - ICD 10 Diagnosis Code of schizophrenia (Organization, 1992). During this six-year period, a total of 567 patients were diagnosed with schizophrenia and 108 patients of these patients (19%) experienced pharmacologically resistant AVH (V. Jónasson et al., 2019).

1.1.2 Diagnosis of schizophrenia

The diagnostic classification systems of schizophrenia are ICD-11 (2018), ICD-10 (1992) and DSM-5 (2013). A comparison between diagnostic classification systems showed that the diagnosis of schizophrenia continues to be based on data obtained through clinical observation rather than on biological markers related to brain function or disease (Valle, 2020). World Health Organization member states meeting at the World Health Assembly adopted ICD-11 in May 2019, and the new ICD version will come into effect in January 2022 (*World Health Assembly Update, 25 May 2019*, n.d.).

At National University Hospital of Iceland Landspítali, the classification of patients with schizophrenia is made based on ICD-10 criteria (V. Jónasson et al., 2019).

i. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)

According to ICD-10 Version 2019, the schizophrenic disorders (*ICD-10 Version:2019*, n.d.) are classified with a billable/specific F20-F20.9 codes and are characterized by:

- Fundamental and characteristic distortions of thinking and perception and affects that are inappropriate or blunted.
- Clear consciousness and intellectual capacity are usually maintained although certain cognitive deficits may evolve in the course of time.
- Psychopathological phenomena include thought echo; thought insertion or

withdrawal; thought broadcasting; delusional perception and delusions of control; influence or passivity; hallucinatory voices commenting or discussing the patient in the third person; thought disorders and negative symptoms.

- The course of schizophrenic disorders can be either continuous, or episodic with progressive or stable deficit, or there can be one or more episodes with complete or incomplete remission.
- The diagnosis of schizophrenia should not be made in the presence of extensive depressive or manic symptoms unless schizophrenic symptoms antedate the affective disturbance. Nor should schizophrenia be diagnosed in the presence of overt brain disease or during states of drug intoxication or withdrawal.

Exclusions are acute schizophrenia (undifferentiated) (F23.2), cyclic schizophrenia (F25.2), schizophrenic reaction (F23.2) and schizotypal disorder (F21).

ii. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5)

According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5) schizophrenia corresponds to Disorder Class: Schizophrenia Spectrum and Other Psychotic Disorders. To diagnose schizophrenia **A-F criteria** were published by the American Psychiatric Association (APA) in 2013 (American Psychiatric Association, 2013):

- Criterion A: Two or more of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (i.e., diminished emotional expression or avolition) are present for a significant period of 1 month. At least one of these symptoms must be delusions, hallucinations, or disorganized speech.
- Criterion B: Impaired level of functioning in work, interpersonal relations, or self-care.
- Criterion C: ***Duration*** of the symptoms describing that continuous signs of the disturbance persist for ***at least 6 months***. This 6-month period must include ***at least 1 month of symptoms*** (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences). The last three criteria D, E, and F are of exclusion of other conditions.
- Criterion D: No Schizoaffective disorder and depressive or bipolar disorder with psychotic features
- Criterion E: No physiological effects of a substance or another medical condition.
- Criterion F: No autism spectrum disorder or a communication disorder of childhood-onset.

All previous subtypes of schizophrenia (paranoid, disorganized, catatonic, undifferentiated, and residual) were dropped from the DSM 5.

iii. ICD-11 for Mortality and Morbidity Statistics (ICD-11 MMS), Version 2021

The new ICD-11 code proposed for schizophrenia is 6A20 and the patients are classified in the subchapter *Schizophrenia or other primary psychotic disorders* of Chapter 06 *Mental, behavioral, or neurodevelopmental disorders*. Exclusions are Schizotypal disorder (6A22), Schizophrenic reaction (6A22), and Acute and transient psychotic disorder (6A23) (*ICD-11 for Mortality and Morbidity Statistics*, n.d.). The description of schizophrenia is characterized by:

- Disturbances in multiple mental modalities, including thinking (e.g., delusions, disorganization in the form of thought), perception (e.g., hallucinations), self-experience (e.g., the experience that one's feelings, impulses, thoughts, or behavior are under the control of an external force), cognition (e.g., impaired attention, verbal memory, and social cognition), volition (e.g., loss of motivation), affect (e.g., blunted emotional expression), and behavior (e.g., behavior that appears bizarre or purposeless, unpredictable or inappropriate emotional responses that interfere with the organization of behavior).
- Psychomotor disturbances, including catatonia, may be present.
- Persistent delusions, ***persistent hallucinations***, thought disorder, and experiences of influence, passivity, or control ***are considered core symptoms***. Symptoms must have persisted for ***at least one month*** for a diagnosis of schizophrenia to be assigned.
- The symptoms are not a manifestation of another health condition (e.g., a brain tumor) and are not because of a substance or medication on the central nervous system (e.g., corticosteroids), including withdrawal (e.g., alcohol withdrawal).

ICD-11 made 3 changes in the characterization of schizophrenia from ICD-10. ICD-11 removed the subtypes of schizophrenia from ICD-10, has introduced a symptom specifier which records information on the presence or absence of symptoms, their longitudinal course, response to treatment and prognosis in the disorder (i.e., positive, negative, depressive, manic, psychomotor, and cognitive deficits), and it modified the ICD-10 schizophrenia course specifier. The course of the disorder in ICD-10 was divided into continuous, episodic (with progressive or stable deficit and remitting), remission (complete and incomplete), other and uncertain course. These specifiers were changed in ICD-11 to the following categories: first episode, multiple episodes, continuous course and unspecified. An important change of the course specifier is the incorporation of the “first episode” category, which will enable better registration in health systems of patients who started with psychotic symptoms and better longitudinal study of the disorder from its initial stages (Valle, 2020).

1.1.3 Treatment plan

After the diagnosis the treatment planning has three goals: reduce or eliminate symptoms, maximize the quality of life and adaptive functioning, and maintain recovery from the debilitating effects of illness to the maximum extent possible (Lehman et al., 2004). These goals are included in the guidelines of the American Psychiatric Association (APA) from 2004. The treatment plan must be focused differently for the acute phase, stabilization phase, and stable phase. During the acute phase, determined by an acute psychotic episode, the goals are to prevent harm, control disturbed behavior, reduce the severity of psychosis and associated symptoms, establish the factors that led to the acute episode, and establish a therapeutic alliance with the patient and family. The stabilization phase goals are to reduce stress on the patient, minimize the likelihood of relapse, reduction in symptoms and consolidation of remission, and promote the process of recovery. The goals of treatment during the stable phase are to ensure

that symptom remission or control is sustained, that the patient is maintaining or improving the quality of life level, that increases in symptoms or relapses are effectively treated, and that monitoring for adverse treatment effects continues (Lehman et al., 2004).

New guidelines were approved after a new meeting of APA in December 2019 (Keepers et al., 2020). The guidelines include a box with recommendations and suggestions for three components: 1) The assessment and determination of the treatment plan, 2) Pharmacotherapy and 3) The psychosocial intervention.

1.1.4 Antipsychotic treatment

APA recommends with ***high support*** of research evidence (1A) that patients with schizophrenia be treated with antipsychotic medication and monitored for effectiveness and side effects and that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with antipsychotic medication. With ***moderate support*** of research evidence (1B), APA recommends that patients with treatment-resistant schizophrenia and those for whom the risk for suicide attempts or suicide remains substantial despite other treatments be treated with clozapine (Keepers et al., 2020). It was observed that 24 weeks of the atypical antipsychotics (risperidone) can improve the symptoms of AVH in healthy individuals who show no other signs of psychiatric illness or history of mental illness (Shan et al., 2019).

1.1.5 Clozapine-resistant schizophrenia and pharmacologically resistant AVH

A uniform definition of treatment resistance in the pharmacotherapy of schizophrenia is not available and most treatment guidelines require the failure of at least two antipsychotic trials with different compounds, including at least one second-generation antipsychotic, in an adequate dose over a period between 2 and 8 weeks before treatment resistance can be assumed (Dold & Leucht, 2014). The concept of treatment-resistant schizophrenia might be defined by three key elements: 1) Confirmed diagnosis of schizophrenia based on validated criteria, 2) Adequate pharmacological treatment, and 3) Persistence of significant symptoms despite adequate treatment (Howes et al., 2017).

Clozapine, a second-generation antipsychotic drug is the gold-standard evidence-based treatment for patients with treatment-resistant schizophrenia due to its superiority over other antipsychotic drugs (Chakos et al., 2001; Dellazizzo et al., 2018).

Although clozapine is considered the most effective antipsychotic agent for patients with refractory hallucinations, not all patients can achieve remission (Kane et al., 1988). The hallucination severity can show a rapid decrease with antipsychotic medication. However, 8% of the first-episode patients go on to experience mild, moderate, or severe hallucinations after they continue their medication as prescribed during 1 year (Sommer et al., 2012).

Patients can be included in the category of clozapine-resistant schizophrenia (CRS) if they present a failure to demonstrate an adequate response to the drug with clozapine plasma levels above 350 ng/ml and a duration of clozapine treatment of a minimum of 8–12 weeks after reaching therapeutic plasma levels (Campana et al., 2021).

Auditory verbal hallucinations (AVH) are referred to the experience of hearing spoken words or sounds in the absence of an actual speechmaker. The AVH are defined as vivid sensations that are generally experienced as voices and are a common symptom of schizophrenia, affecting 60-80% of patients (Sartorius et al., 1986; Waters & Fernyhough,

2019). Up to 30% of the patients with schizophrenia may be treatment-resistant and suffer from persistent psychotic symptoms, notably auditory verbal hallucinations (AVH) (Sartorius et al., 1986).

1.1.6 Nonpharmacological intervention

The actual treatment plan and the new APA guidelines described above (Keepers et al., 2020) are not including any of the non-pharmacologically or non-psychological interventions (e.g., neurofeedback, RTMS).

The use of cognitive-behavioral therapy remains the most used psychological intervention. With moderate support of research evidence (1B), APA recommends that patients with schizophrenia be treated with cognitive behavioral therapy for psychosis (Keepers et al., 2020). According to the cognitive model of AVH, which is the basis of cognitive-behavioral therapy for psychosis (CBTp) (Chadwick & Birchwood, 1994), it is not the voice nor its contents that causes anxiety, but rather the way the patient evaluates it. Group treatment of auditory hallucinations (Wykes et al., 1999) and avatar therapy (Dellazizzo et al., 2018) show a significant decrease in auditory hallucinations, as measured by the PSYRATS scale (Langlois et al., 2020). A meta-analysis including eighteen randomized controlled trials of CBT versus a control condition in 1418 patients showed that CBTp was effective in treating auditory hallucinations showing a significant effect-sizes ranging from 0.31 to 0.49 (Van der Gaag et al., 2014).

For ultra-resistant patients with schizophrenia, also known as clozapine-resistant schizophrenia (Campana et al., 2021) several treatment strategies are available, including psychotherapy, pharmacological augmentation, repetitive transcranial magnetic stimulation (RTMS), and electro-convulsive therapy (ECT) (Sommer et al., 2012).

1.2 Neurophysiology

Neurophysiology is a subdiscipline of the scientific disciplines' physiology and neurosciences and it is devoted to the functional analysis of the peripheral and central nervous system applying a variety of experimental and clinical methods (Luhmann, 2013b). The word originates from Greek *physiologia* "natural science, inquiry into nature," from physios' "nature" + logia "study" meaning "science of the normal function of living things". To this is added the prefix neuro- from the Greek word *neura* meaning "nerve" (*Physiology | Etymology, Origin and Meaning of Physiology by Etymonline*, n.d.).

Clinical neurophysiology is a medical specialty that studies the central and peripheral nervous systems through the recording of bioelectrical activity, whether spontaneous or stimulated. Clinical neurophysiology uses techniques that are diagnostically or pathophysiologically oriented. The quantitative results are obtained with standardized techniques, distributed worldwide, and offer precise norms that can be used to match the results obtained in one given patient. Sometimes, a battery of complementary tests can be applied to one patient enabling the physician to judge the coherence between the results. The most used techniques are electroencephalography, spectral EEG, cortical mapping, motor potentials, cortical stimulation, brainstem auditory potentials, visual evoked potentials, blink reflex, somatosensory evoked potentials, spinal conduction velocity, H reflex, F waves, needle electromyography, repetitive nerve stimulation (Delwaide & Pennisi, 1992), repetitive transcranial magnetic stimulation (RTMS), intraoperative neuromonitoring (IONM), and video polysomnography.

1.2.1 Electroencephalography

The EEG measures the electrical activity produced by the brain surface or cerebral cortex, which is recorded with electrodes (Luhmann, 2013a). It records the synchronized activity of excitatory (EPSPs) and inhibitory postsynaptic potentials (IPSPs) in the cerebral cortex and displays the activity as voltage amplitude changes over time. Negative (upward) deflections are due to superficial excitatory or deep inhibitory inputs, whereas positive (downward) deflections represent deep excitatory or superficial inhibitory inputs (Kirschstein & Köhling, 2009).

i EEG frequencies

The neuron cell action potentials are too short to sufficiently sum up and be observed over the scalp level. The scalp EEG detects postsynaptic potentials with up to 10 ms duration which can produce potential changes at the extracellular level (Kirschstein & Köhling, 2009). The synchronized activity of excitatory (EPSPs) and inhibitory postsynaptic potentials (IPSPs) in the cerebral cortex are recorded as voltage amplitude changes over time (Wang et al., 2015).

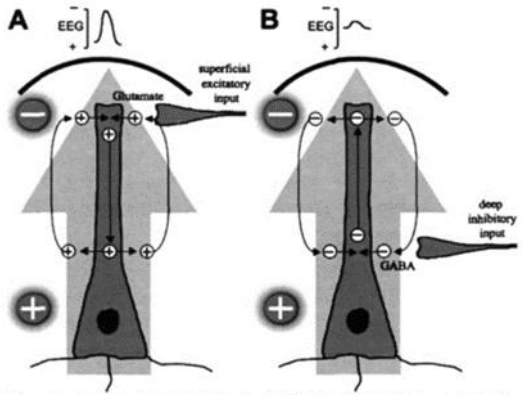
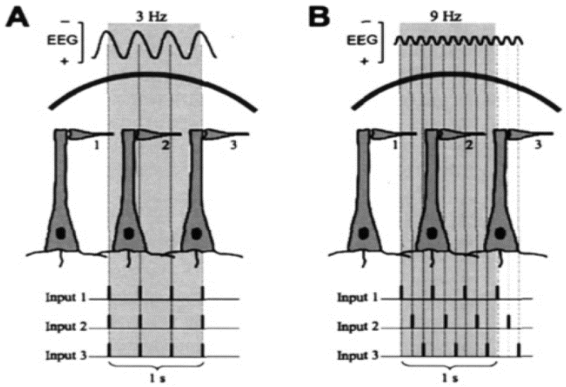


Figure 1-1 *Negative (upward) deflections are due to superficial excitatory inputs (A) or deep inhibitory inputs (B) to the pyramidal neurons. Permission of reuse is granted for use of content in a Doctoral Dissertation. Article: What is the Source of the EEG? Author: Timo Kirschstein, Rüdiger Köhling, Publication: Clinical EEG and Neuroscience, Publisher: SAGE Publications, Date: 07/01/2009 Copyright © 2009, © SAGE Publications*

The EPSP (e.g., synapses with glutamate as the neurotransmitter) is a positive potential at the postsynaptic membrane (depolarization). The presynaptic action potential opens voltage gated Ca2+ channels, and the presynaptic Ca2+ influx causes the glutamate release stored in presynaptic vesicles. Glutamate binds to specific postsynaptic receptors and leads to a Na+ and Ca2+ influx producing the positive excitatory postsynaptic potential, which is negative at the extracellular space (**Figure 1-1**, A), due to the preponderance of negative charge carriers.

The IPSP is observed in GABAergic synapses (**Figure 1-1**, B). The most important inhibitory neurotransmitter, γ-aminobutyric acid (GABA), binds to GABAA and GABAB receptors. Ionotropic GABAA receptors are chloride (Cl−) channels and mediate a Cl− influx, whereas metabotropic G protein-coupled GABAB receptors induce a K+ outward current. Together, this produces a stronger negative membrane potential (hyperpolarization) which at the extracellularly level is positive due to positive charge carriers (Kirschstein & Köhling, 2009). At the cortical level, both EPSP and IPSP are negative with different amplitudes, IPSP being reduced due to more distal input (**Figure 1-2**).

The usual classification of the main EEG rhythms based on their frequency ranges is as follows: delta 2-4 Hz, theta 4-8 Hz, alpha 8-13 Hz, beta 13-30 Hz, and gamma - higher than 30 Hz. EEG oscillations contribute to different cognitive functions depending on where in the brain and with what parameters (amplitude, frequency, phase, coherence) they occur (Herrmann et al., 2016). Alpha rhythm could be generated by intracortical networks involving layer V pyramidal neurons of the visual cortex, the latter being the main potential sources (Lopes Da Silva & Storm Van Leeuwen, 1977). The theta rhythms are believed to correspond to



interactions between cortical and hippocampal neuronal groups (Miller, 1994). The neuronal oscillators, which generate the beta rhythm, presumably are located inside the cortex (Lopes da Silva, 1991). Gamma oscillations might represent interneuronal feedback between hemispheres, with the highly irregular firing of pyramidal neurons. The long-range interneurons may be critical for gamma-phase synchrony in different brain regions (Buzsáki & Wang, 2012).

Figure 1-2 *Synchronization (A) and desynchronization (B) is shown for three pyramidal neurons each of them receiving one superficial excitatory input (EPSP). Permission of reuse is granted for use of content in a Doctoral Dissertation. Article: What is the Source of the EEG? Author: Timo Kirschstein, Rüdiger Köhling, Publication: Clinical EEG and Neuroscience, Publisher: SAGE Publications, Date: 07/01/2009 Copyright © 2009, © SAGE Publications*

Gamma oscillations have been associated with functional inhibition, cortical activation, information processing, conscious perception, and maintenance of memory contents (Herrmann et al., 2016).

ii Relative power

The frequency-domain analysis uses the Fast Fourier Transform (FFT) algorithm to calculate absolute power (μV2/Hz), relative power (%), and mean frequency (Hz) within each of the sub-bands. The absolute power of a band is the integral of all the power values within its frequency range. The relative power (RP) is derived by expressing absolute power in each frequency band as a percent of the absolute power (AP) summed over all frequency bands (Yuvaraj et al., 2014a). Power spectral density (PSD) analysis is a type of spectral analysis performed when random effects obscure the desired underlying phenomenon.

iii “Bird-eye” view EEG. Topographical maps of the relative power

EEG recordings can be performed during the resting-state (Y. J. Kim et al., 2017; Wang et al., 2015) or during a given task (Fernández et al., 1995). The oscillations (measured at scalp level EEG) originate from synchronized pyramidal cell activity at the cortical level (delta-alpha range) as shown in **Figure 1-2**, A. This synchronization is caused by afferent inputs from thalamic nuclei (Steriade et al., 1993). The EEG becomes desynchronized when this slow oscillatory activity breaks up and is replaced by a signal with higher frequencies and lower amplitude (beta-gamma range) (**Figure 1-2**, B). In normal participants, event-related desynchronization (ERD) and event-related synchronization (ERS) are considered to indicate the activation and subsequent recovery of the motor cortex during planning, executing, and completing a movement (Pfurtscheller & Aranibar, 1977). ERD and ERS are different responses of neuronal structures in the brain and are both time-locked to the event (Aoh et al., 2019).

A “bird-eye” view map is nowadays a term used to describe a topographical map of the brain seen from above, with the *nasium* anteriorly. Quantitative power spectral EEG maps of the absolute and relative power of different EEG frequency bands have been used to compare a group of patients and healthy controls, patients before and after treatment, subjects during a task with the resting state (Fernández et al., 1995; Y. J. Kim et al., 2017; Wang et al., 2015), or just as a complementary diagnostic tool for neurological diseases like stroke, brain tumor or spinocerebellar ataxia (Aoh et al., 2019; Psatta, 2000). This method may be the most suitable for measuring vigilance, as it allows objective and quantitative evaluation of the brain regions

(Saletu et al., 2005). Histogram graphs of absolute and relative power can be used to detect outliers (Fernández et al., 1995) before data interpretation on group levels.

The question is how effective and reliable the EEG absolute and relative power is to assess the effects of medication or other noninvasive therapeutic interventions. Is this a valid biomarker to detect long-lasting effects on neural behavior response?

A good example of the "bird-eye" view map and the usefulness of the QEEG is the study of Kim et al (Y. J. Kim et al., 2017). In their study, 20 patients with internet gaming disorder (IGD) were assessed before and after 6 months of pharmacotherapy with selective serotonin reuptake inhibitors (SSRI). A minimum of 20 to 60 seconds of EEG data during resting state

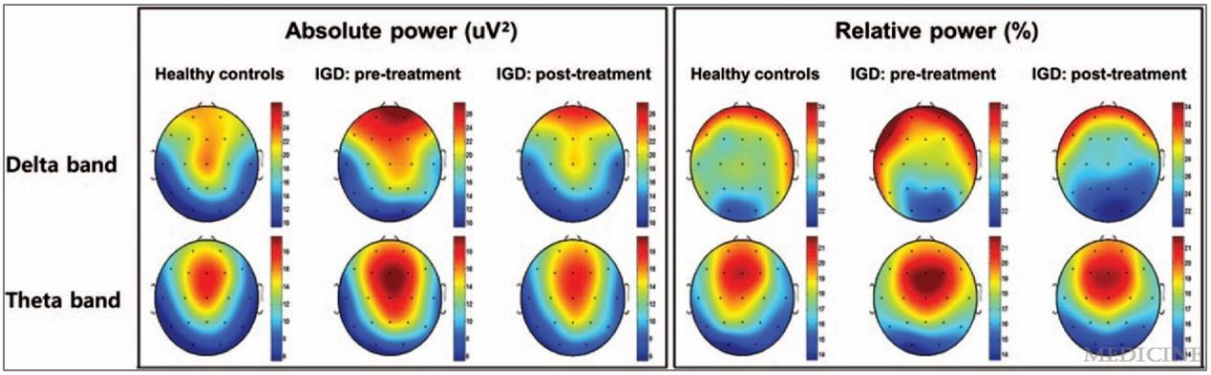


Figure 1-3 *Topographical maps of the absolute and relative powers in patients with Internet gaming disorder (IGD) before and after the 6-month treatment with SSRI. Reprinted with permission from Wolters Kluwer Health, Inc.: Kim, Yeon Jin; Lee, Jun-Young; Oh, Sohee; Park, Minkyung; Jung, Hee Yeon; Sohn, Bo Kyung; Choi, Sam-Wook; Kim, Dai Jin; Choi, Jung-Seok. "Associations between prospective symptom changes and slow-wave activity in patients with Internet gaming disorder" Medicine96(8): e6178, February 2017. doi: 10.1097/MD.0000000000006178., License date Nov 04, 2021*

was selected for the spectral analysis, and the absolute and relative power for the accepted epochs were calculated with fast Fourier transforms. The EEG activity was analyzed from 19 selected sites that were divided into 3 regions by averaging within each region: frontal (7 electrodes), central (5 electrodes), and posterior (7 electrodes) (Y. J. Kim et al., 2017). Compared with the healthy control group (N29), the authors observed, before the treatment, an increased global absolute power of the delta band ($p = 0.046$) and in the theta band of the central brain region ($p = 0.021$) (**Figure 1-3**). Following 6 months of treatment, the absolute power in the delta band of the frontal region of the IGD group exhibited a significant reduction compared with baseline ($p=0.043$), and the extent of this decrease was significantly correlated with change in Young's Internet Addiction Test (IAT) score ($r=0.57$, $P=0.011$).

iv Graph theory and network organization

Graph theory is a branch of mathematics and combinatorics with many applications in diverse fields, ranging from physics, communication science, and electrical engineering to genetics, linguistics, and sociology (Sporns, 2003). Graphs are mathematical structures used to model pairwise relations between objects. A graph in this context is made up of vertices or ***nodes*** which are connected by edges or ***links***. A distinction is made between undirected graphs, where edges link two vertices symmetrically and directed graphs, where edges link two vertices asymmetrically[3].

The Swiss mathematician Leonhard Euler is considered the pioneer of graph theory and topology after he solved a popular puzzle about bridges in 1735 (Newman, 2003). The East Prussian city of Königsberg (now Kaliningrad) occupies both banks of the River Pregel and an island, Kneiphof, which lies in the river at a point where it branches into two parts. There were

[3] https://sapienlabs.org/graph-theory-in-eeg/

seven bridges[4], and the question was how could a person cross each of the seven bridges only once and return home? Long thought to be impossible, the first mathematical demonstration

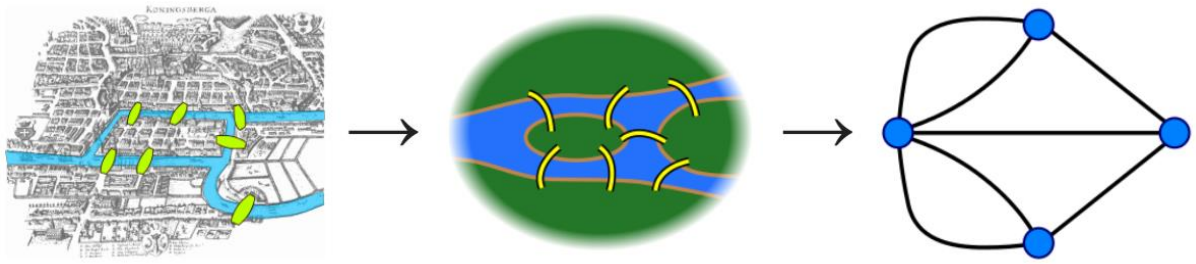


Figure 1-4 *The Seven Bridges of Königsberg. File licensed under the Creative Commons Attribution-Share Alike 3.0 Unported*

that this is impossible was presented by Euler to the members of the Petersburg Academy on August 26, 1735 (Alexanderson, 2006) using a graph (**Figure 1-4**).

A network can be described as a graph G = (V, E), where V denotes the set of nodes and E is the set of links. There are four types of network topology, including weighted undirected, weighted directed, binary undirected, and binary directed (e.g., functional connectivity network is represented by a weighted undirected graph).

The computational analysis of brain structural and functional connectivity patterns represents one of the main contributors in understanding the role of brain dynamics in perception and cognition. To allow mathematical analysis, neuronal connectivity patterns (networks) are represented as graphs. All graph theory methods are based on a network's connection (adjacency) matrix, which in brain dynamics can be derived from several different sources like databases of cortico-cortical and cortico-thalamic pathways (Sporns, 2003). The adjacency matrix contains binary entries (i.e., aij). The entry aij = 1 if the connection from j to i is present, and aij = 0 if the connection is absent and, all-zero being the main diagonal. An important concept in graph theory is the path. ***Paths*** are all ordered sequences of distinct edges and vertices, linking a source vertex j to a target vertex i. If j=i, the corresponding paths link the source vertex to itself and are called ***cycles*** (Rubinov & Sporns, 2010; Sporns, 2003).

In 1998, Watts and Strogatz described the randomness of complex networks, a phenomenon related to the networks often seen in nature showing an organizational pattern between regular and random states. This network organization in between regular and random states was named small worldness (SW) (Watts & Strogatz, 1998). Small-world networks represent the shortest path (minimum number of edges) along the existing edges (links) between each pair of nodes in the network. In small-world networks, the clustering coefficient (i.e., the abundance of connected triangles in a network) is high, and the average path length is short (Farahani et al., 2019). The SW index is calculated by the clustering coefficient (C) and the characteristic path length (L) ratio by size-matched L/L(random) network (Watts & Strogatz, 1998). In network analysis, the measures can be represented for individual elements (such as nodes or links) reflecting the way in which these elements are embedded in the network (e.g., participation coefficient) or for all individual elements, which provides a more global description of the network. A basic and important measure is known as the ***degree*** of an individual node which is equal to the number of links connected to that node (Rubinov & Sporns, 2010). Graph theory has great applications in brain networks analysis. The networks which show the ability for specialized processing to occur within densely interconnected groups of brain regions are characterized by segregation and the main measures for ***network segregation*** are the clustering coefficients and modularity (Cao et al., 2016). If the networks show the ability to rapidly combine specialized information from distributed brain regions, they

[4] Seven bridges of Königsberg

are characterized by ***functional integration*** and they are better measured by quantifying the flow between pairs of brain regions (e.g., ***length of path***) (Rubinov & Sporns, 2010). The average shortest path length between all pairs of nodes in the network is known as the characteristic path length (Watts & Strogatz, 1998) (**Figure 1-5**).

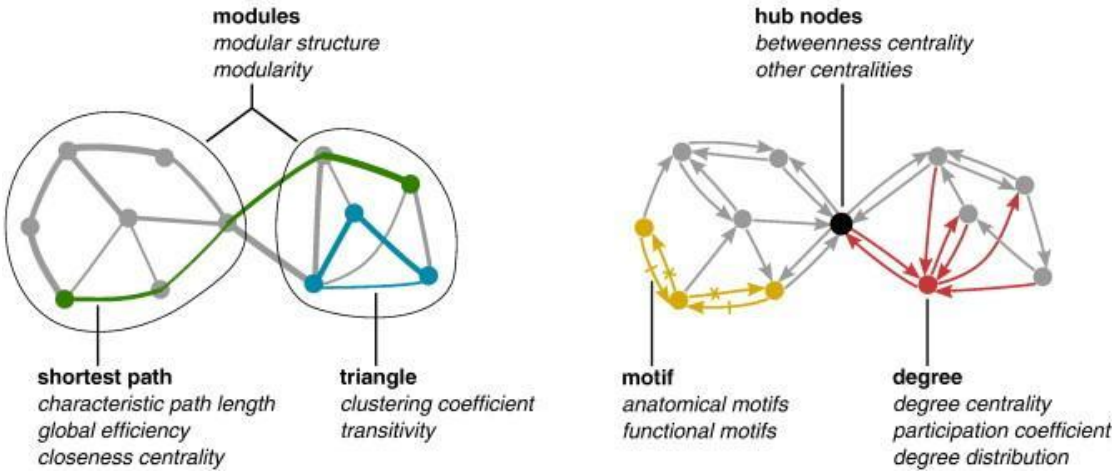


Figure 1-5 *Measures of network topology. Measures of integration are based on shortest path lengths (green), while measures of segregation are based on triangle counts(blue). Measures of centrality may be based on node degree (red). Hub nodes (black) often lie on a high number of shortest paths and consequently often have high betweenness centrality. Patterns of local connectivity are quantified by network motifs (yellow). Reprinted from Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. NeuroImage, 52(3), 1059–1069 with permission from Elsevier. License date Nov. 5, 2021.* *https://doi.org/10.1016/J.NEUROIMAGE.2009.10.003*

Graph theory measures are a modern tool to investigate the neurobiological inferences regarding the mechanisms underlying human cognition and behavior related to brain disorders (Farahani et al., 2019). The most used graph tools for characterizing the functional brain

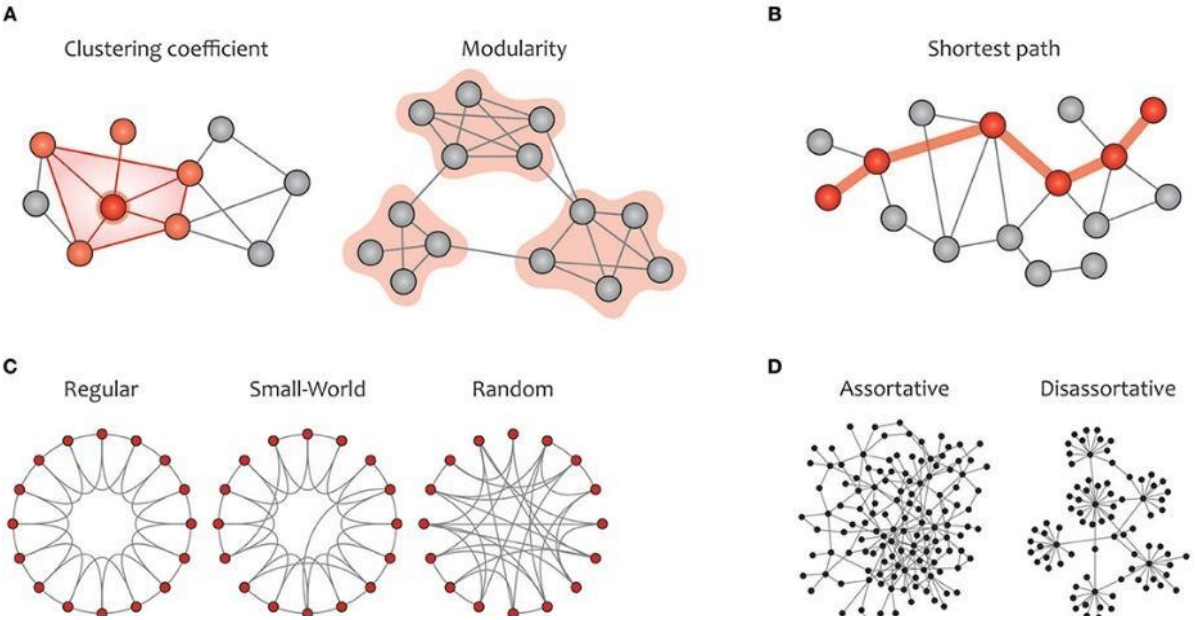


Figure 1-6 *Summary of* ***global (graph) measures****. (A) Segregation measures include clustering coefficient, which quantify how much neighbors of a given node are interconnected, modularity, which is related to clusters of nodes, called modules. (B) Integration measure include characteristic path length, determined as the average shortest path length across all pairs of nodes. (C) A small-world network (middle) illustrates an intermediate balance between regular and random networks reflecting a high clustering coefficient and a short path length. (D) The assortativity index measures the extent to which a network can resist failures in its main components. Reprinted with permission granted from Dr. Waldemar Karwowski, Nov 6th, 2021. Copyright © 2019*

network are categorized in metrics describing global or local properties. These metrics are applicable to undirected binary, weighted (the links between vertices can take different values) or directed (the links between vertices carry directional information) graphs.

Key topological properties and metrics that characterize the architecture of the brain network connectivity and their corresponding formulas can be obtained using the Brain Connectivity Toolbox[5].

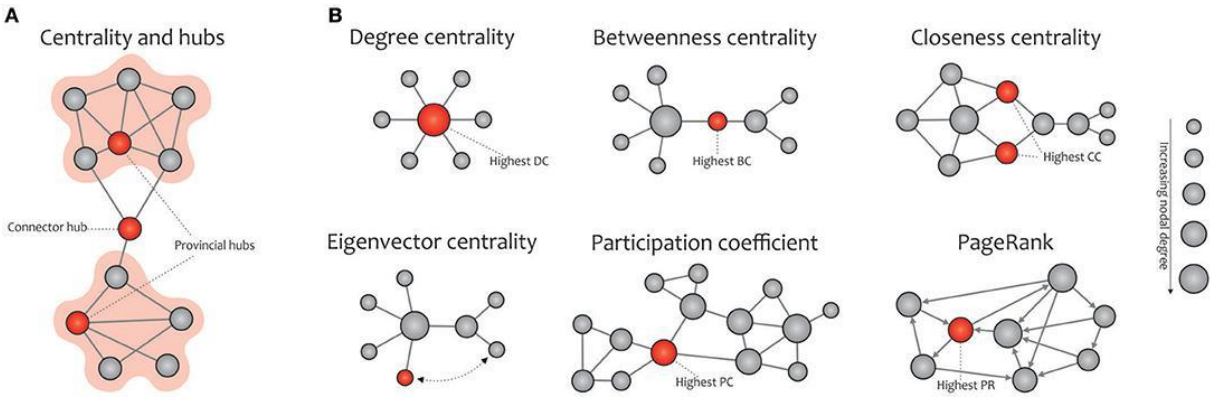


Figure 1-7 *Summary of* ***local (graph) measures****. Participation coefficient (a metric we used in Study 3) is a characteristic of a node and represents the distribution of its connections among separate modules. Reprinted with permission granted from Dr. Waldemar Karwowski, Nov 6th, 2021. Copyright © 2019*

A regular network displays a high clustering coefficient and a long average path length, while a random network displays a low clustering coefficient and a short average path length. A small-world network illustrates an intermediate balance between regular and random networks reflecting a high clustering coefficient and a short path length (Watts & Strogatz, 1998). Brain neural networks in patients with schizophrenia were found to be characterized by dysconnectivity and altered network connectivity was suggested as a potential endophenotype of schizophrenia (P. Li et al., 2017; Lynall et al., 2010).

[5] https://sites.google.com/site/bctnet/measures

1.2.2 Event-related potentials and sensory gating

Event-related potentials (ERPs) are EEG changes that are time-locked to the sensory, motor, or cognitive events that provide a safe and noninvasive approach to study psychophysiological correlates of mental processes. ERPs in humans can be classified as 'sensory' or 'exogenous' within the first 100 milliseconds after the stimulus and 'cognitive' or

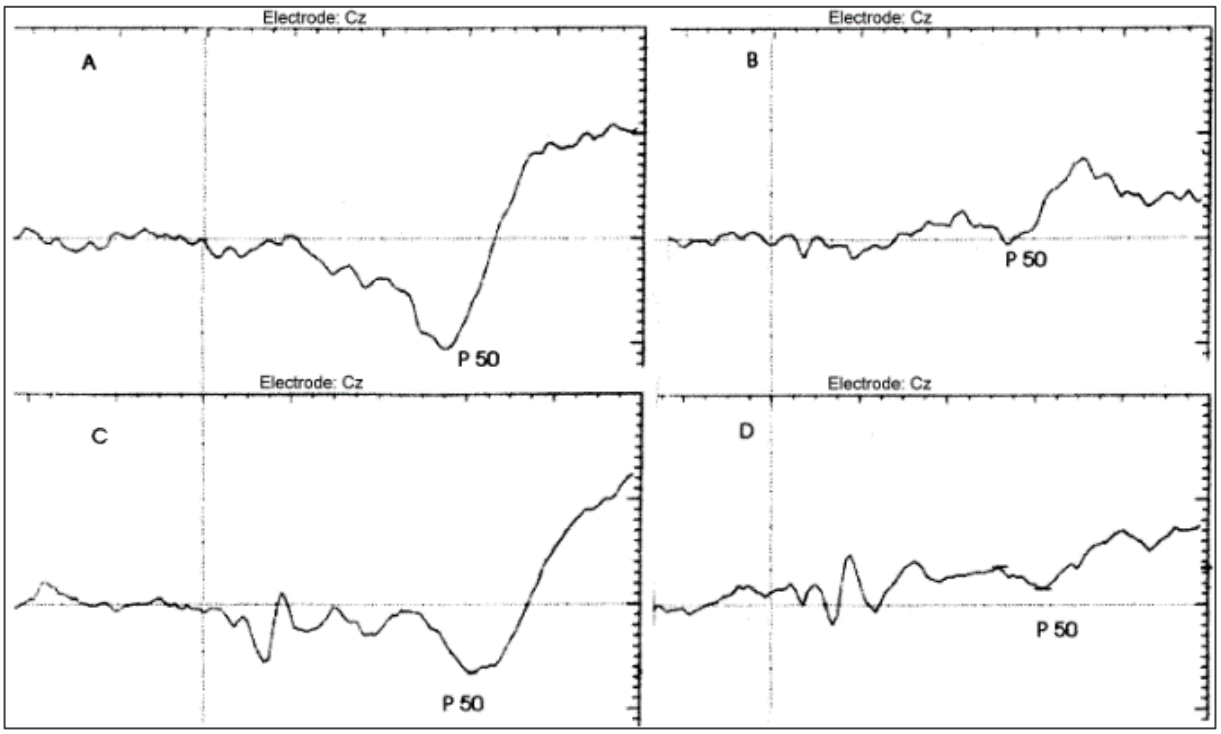


Figure 1-8 *Representative examples of the P50 of the first and second click of a single subject after placebo (A,B) and after diazepam (C,D). X-axis div = 5ms. Reprinted from Neuroscience Letters Volume 341, Issue 1, Author: Gilles van Luijtelaar, The effects of diazepam on sensory gating in healthy volunteers, Pages 65-68, ISSN 0304-3940, https://doi.org/10.1016/S0304-3940(03)00155-1. Copyright © 2003, with permission from Elsevier. License date Nov 15, 2021*

'endogenous' ERPs as they examine information processing (Sur & Sinha, 2009). According to their latency and morphology, the waves are named with "N" if the component is a negative wave or with "P" if the component is a positive wave (e.g., N100 is a negative component at 100 ms). In some works, the ERP components are presented following the similar rule like in EEG, with upward negativity (Van Luijtelaar, 2003), while other studies present the negative components with a downward deflection like the negative Q wave from the electrocardiogram ventricular complex (*Understanding the Normal ECG | Thoracic Key*, n.d.).

i Mid latency auditory evoked potentials (MLAEP)

The MLAEPs have been reported to be abnormal in several psychiatric disorders, but most prominently schizophrenia. Buchsbaum used the term middle evoked response components to describe three components in a positive, negative, positive sequence. These waves were P100 at 50–100 ms, N140 at 110–140 ms, and P200 at 160–200 ms (Buchsbaum, 1977). Later, the term mid-latency was used to describe potential components occurring between 50 and 200 ms and these components are P50, N100, and P200 (Nash N Boutros et al., 2006). It was suggested that latency reflects the complexity and efficiency of the synaptic pathway mediating the response and speed of information processing and that amplitude

represents the sum of the cerebral resources allocated to a response. The relation between the topography and the morphology of these components has not been fully elaborated (Nashaat N Boutros et al., 2004).

ii P300

The P300 wave or the P3 component was discovered in 1965 (Sutton et al., 1965) and since then has been the major component of research in the field of ERP. For auditory stimuli, the latency range is 250-400. The latency is usually interpreted as the speed of stimulus classification, shorter latencies indicating superior mental performance relative to longer latencies. P3's higher amplitude seems to reflect greater attention (Sur & Sinha, 2009). P300 is usually recorded during two-tone discrimination (oddball) tasks. The waves N100, P200, N200, P300 are elicited by the rare stimuli, whereas frequent stimuli elicit only N100 and P200 (Ogura et al., 1991). The mean amplitudes of the N100 and P300 auditory responses were decreased in patients with schizophrenia in comparison to the healthy participants (Earls et al., 2016; Ogura et al., 1991).

iii Sensory gating

The effective processing of sensory information includes the ability to gate out or inhibit neuronal responses to sensory information that has been coded as redundant or irrelevant. This predominantly preconscious neuronal level process is referred to as sensory gating. The P50, an early (~50 ms) positive potential, is used to physiologically index the sensory gating (Adler et al., 1985). Subjects are presented pairs of identical auditory stimuli, whereby the first auditory stimulus (S1) initiates an inhibitory process in the brain which modifies the amplitude of the P50 to the second stimulus (S2) which usually is suppressed (Aidelbaum et al., 2018) (**Figure 1-8**).

Sensory gating deficits were found in schizophrenia (Adler et al., 1985) and have been studied mostly with P50, which likely reflects pre-attentive information processing (Thoma et al., 2017). Alterations in P50 gating are not always related to cognitive deficits (Sánchez-Morla et al., 2008) or to the expression of positive and negative symptoms (Potter et al., 2006).

1.2.3 Transcranial magnetic stimulation and RTMS

i Mechanisms of TMS

Transcranial electrical stimulation (TES) in the non-exposed human cortex was performed with a short current duration and one high-voltage discharge to avoid discomfort and pain (Merton & Morton, 1980). The non-invasive transcranial magnetic stimulation (TMS) was developed in 1984 (Barker et al., 1985). During the procedure of TMS, a coil is placed near the head of the person receiving the treatment. The physical principles were already discovered by the English scientist Michael Faraday in 1831, who first transformed electrical energy into mechanical energy (Poyser, 1892) and later showed that a pulse of electric current passing through a coil made of wire can generate a magnetic field (Heshmati, 2017).

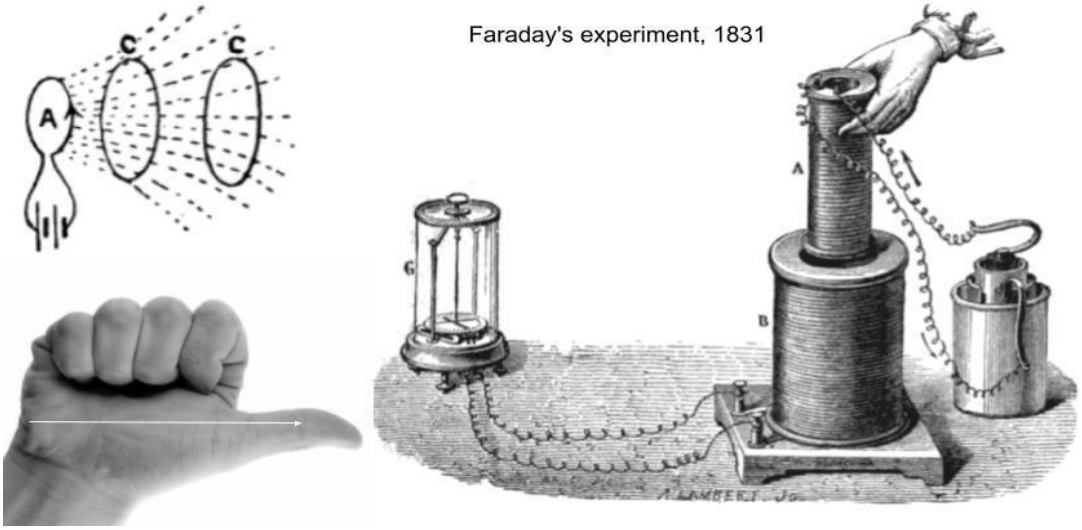


Figure 1-9 *Faraday's experiment. Coil right-hand rule: When the fingers are curled to point in direction of conventional current flow (I) around the core, the thumb points in the direction of the magnetic field. Modified (Poyser, 1892 p.285), public domain.*

A magnetic field in a coil is induced by an electric current from a capacitor discharging through it. The changing magnetic field in the coil reaches the brain surface and induces an

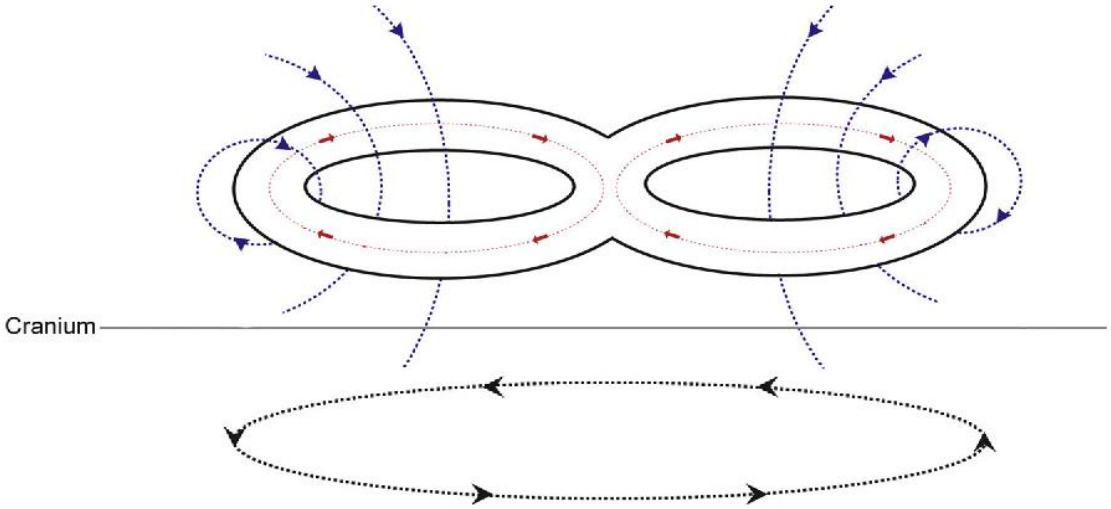


Figure 1-10 *Simplified diagram of the electrical and magnetic fields generated during TMS. Reprinted from Neurosurgery Clinics of North America, 25(4), 819–832.Young, Nicole A.; Sharma, Mayur; Deogaonkar, Milind (2014). Transcranial Magnetic Stimulation for Chronic Pain with permission from Elsevier. License date Oct 30, 2021*

electric current which will depolarize cortical neurons. In **Figure 1-9** it is shown the experiment of Faraday: The liquid battery (right) provides a current which flows through the small coil (A), creating a magnetic field. When the coils are stationary, no current is induced in the larger coil (B). But when the small coil is moved in or out of the large coil (B), the magnetic flux through the large coil changes, inducing a current which is detected by the galvanometer (G) (Poyser, 1892).

In the same way, the magnetic field induced in the coil used for RTMS rises instantaneously to its maximum when the capacitor discharges electrical current (Rothwell, 1997) (**Figure 1-10**). The coil can be *monophasic* with a switch or a diode that determine the current and magnetic field to rise and fall to zero or *biphasic* when the inductance and resistance of the circuit are set so that the first rise and fall of the coil current is the major component of the stimulating electrical field, with subsequent oscillations being dampened effectively (Terao & Ugawa, 2002). It has been suggested that there is preferential activation of the horizontally positioned cells within the cortex when the coil is placed tangentially to the scalp. The

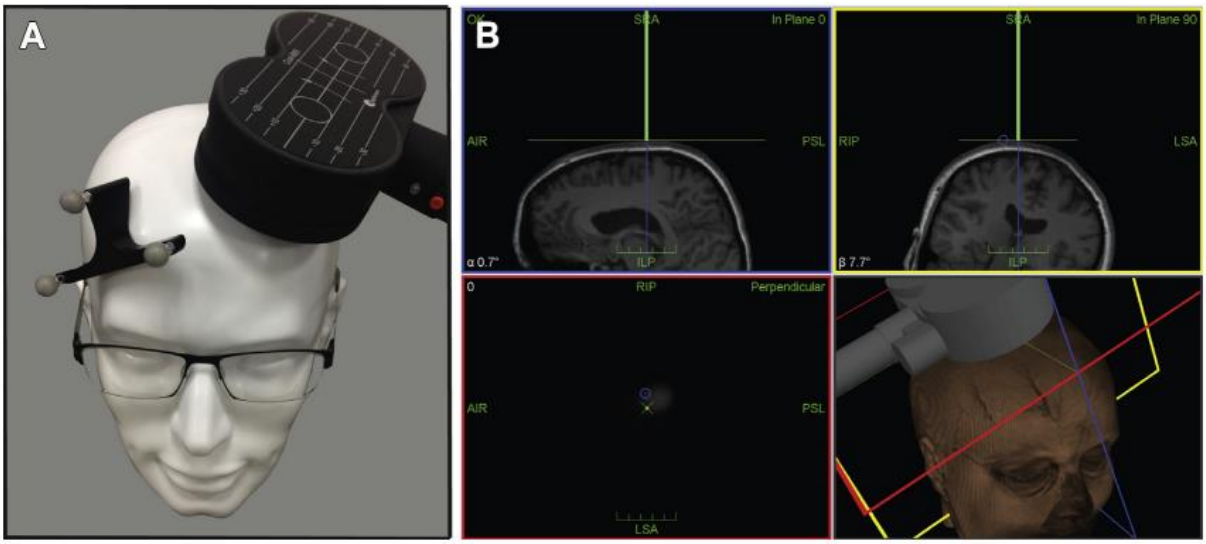


Figure 1-11 *(A) The positioning of a wire coil (MagVenture) to motor cortex. (B) Identifying stimulation site with Localite. Reprinted from Neurosurgery Clinics of North America, 25(4), 819–832.Young, Nicole A.; Sharma, Mayur; Deogaonkar, Milind (2014). Transcranial Magnetic Stimulation for Chronic Pain with permission from Elsevier. License Oct 30,2021*

interneurons are supposed to be preferentially stimulated while cortical pyramidal neurons are activated trans-synaptically because of their vertical orientation within the cortex (**Figure 1-11**) (Young et al., 2014b).

ii Safety guidelines

A consensus conference about the safety of TMS, promoted and supported by the International Federation of Clinical Neurophysiology (IFCN), took place in Siena (Italy) in October 2018. Within main resolutions, it is stated that the TMS research in humans should be conducted under a protocol that is approved by an Institutional Review Board (IRB) or relevant research ethics committee. Informed consent should be obtained by an individual listed on the research protocol who is authorized to obtain informed consent. The protocol will specify the level of risk, the risk-benefit ratio, the roles of each member of the study team, the degree of medical supervision required based on the anticipated risks of the specific protocol. In clinical settings, the decision about prescribing the therapeutic use of TMS for the treatment of a clinical disorder outside of the research context should always be made by an adequately trained

physician, and informed consent for the therapeutic use of TMS should be obtained by a physician. TMS may be delivered by the physician or by an appropriately trained individual who must operate under the supervision of the physician in a context where anticipated side effects may be appropriately managed (Rossi et al., 2021).

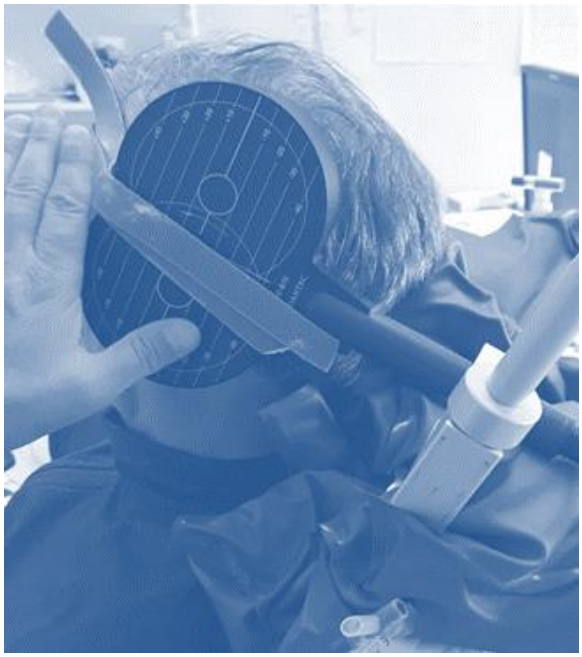


Figure 1-12 *RTMS applied at left temporo-parietal region (T3-P3) using a mechanical arm. Copyright 2021 © Neurophysiology Plus Iceland, OC Banea*

Safety issues for operators exposed to magnetic fields are not frequently addressed. Occupational exposure has been measured for MRI units (Kanal et al., 2012; Riches et al., 2014) regarding the TMS exposure. It was suggested that the clinical staff should not work at distances closer to 0.7 m from the transducer to avoid risks of overexposure to magnetic pulses, a recommendation that is valid for both single coil and figure-8 transducers, due to basic field symmetry considerations. The equipment could be used with a mechanical arm holding the transducer in the right position for the patient (**Figure 1-12**) (Karlström et al., 2006).

iii Clinical applications of RTMS

Level A evidence (definite efficacy) was reached for neuropathic pain, depression, and post-acute stage of stroke. Level B evidence (probable efficacy) was reached for improving quality of life or pain in fibromyalgia; for improving motor impairment or depression, respectively, in Parkinson's disease or for promoting motor recovery at the post-acute stage of stroke; for lower limb spasticity in multiple sclerosis; in posttraumatic stress disorder and in chronic post-stroke non-fluent aphasia. Level A/B evidence was not reached concerning the efficacy of RTMS in any other condition (J. P. Lefaucheur et al., 2020).

1.2.4 Auditory-motor task to trigger gamma oscillations

Resting-state EEG studies in schizophrenia patients show abnormal oscillations in a distributed network of the frontal, temporal and occipital brain regions involved in visual and auditory information. The beta and gamma frequency bands show more independent local organizations in clusters that do not connect with other regions (Tanaka-Koshiyama et al., 2020). For the resting-state EEG analysis, the lack of standardized preprocessing and parameter choices within eyes opened or eyes closed conditions, have resulted in a diversity of results, some of which are mutually contradictory (Newson & Thiagarajan, 2019). Therefore, conditions with more engagement of gamma and beta activity would help to quantify better the EEG changes. Studies have shown that evoked (stimulus-locked) and induced ("triggered" but not locked to stimuli) beta and gamma activity can be elicited during visual discrimination (Lachaux et al., 2000) or auditory cued movement (Nagasawa et al., 2010).

Using subdural electrodes to study free of epileptiform activity EEG segments in patients with epilepsy it was observed that during a simple auditory-motor task the auditory-verbal stimuli elicited augmented gamma-oscillations in the posterior portion of the superior temporal gyrus, whereas hand-motor responses elicited gamma-augmentation in the pre and postcentral gyri (Nagasawa et al., 2010). A left-lateralized region in the posterior Sylvian fissure at the parietal-temporal boundary showed particularly robust MEG (magnetoencephalography) (Levelt et al., 1998) and electrocorticography (Kambara et al., 2018) gamma-band responses to both sensory and motor phases of visual picture naming and auditory naming tasks. These tasks are related to the working memory (WM). The high gamma activity was higher prior to motor cortex activity or speech articulation. The auditory-motor integration circuit is represented by a small set of areas in the superior temporal and temporoparietal cortex, temporal, and frontal areas (Hickok et al., 2003). During naming task judgement, left middle-frontal activation appeared to be well-attributable to WM scanning function, whereas left orbitofrontal activation may be attributable less to WM scanning but more largely to syntactic/semantic processing (Kambara et al., 2018). It was observed that during picture naming test, a region in the left posterior temporal lobe showed prominent activation (i.e., peak activity of dipole sources in the individual magnetic response) starting about 200 msec after picture onset and peaking at about 350 msec, with congruent consistent activation in the right parietal cortex, peaking at about 230 msec after picture onset, thus preceding and partly overlapping with the left temporal response (Levelt et al., 1998).

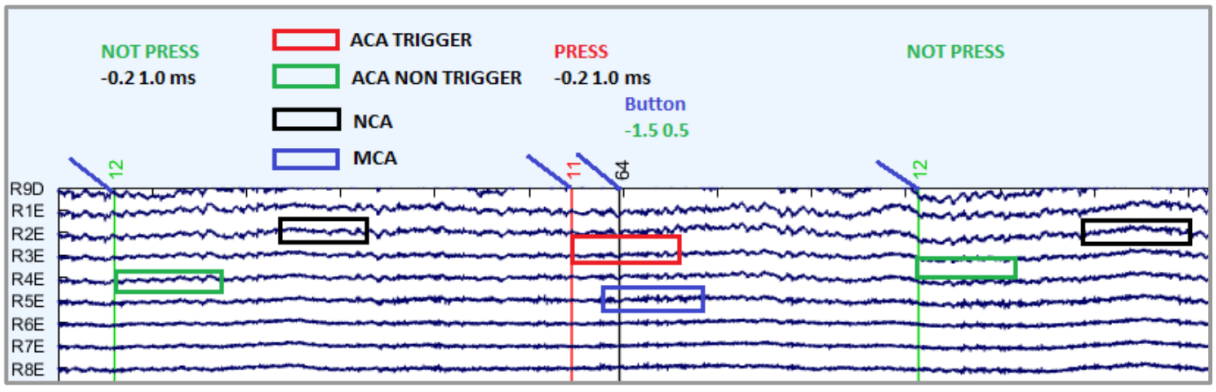


Figure 1-13 *First schematic representation of ACA, MCA and NCA epochs during the auditory-motor task. ACA and NCA epochs length were set initially with 1 sec with 200 ms baseline correction. MCA was set 500 ms after Hand Reaction.*

AVH-TMS Icelandic study[6,7] started in summer 2018 with the first healthy subjects resting-state EEG recordings. Right after, we added to the protocol the auditory-motor task employed by Nagasawa et al (2010) with the hope to trigger gamma oscillations and observe the cortical distribution of this activity. Our intention was to quantify the changes before and after left temporoparietal RTMS treatment in patients with schizophrenia and AVH using the relative power measurements during the auditory-motor task.

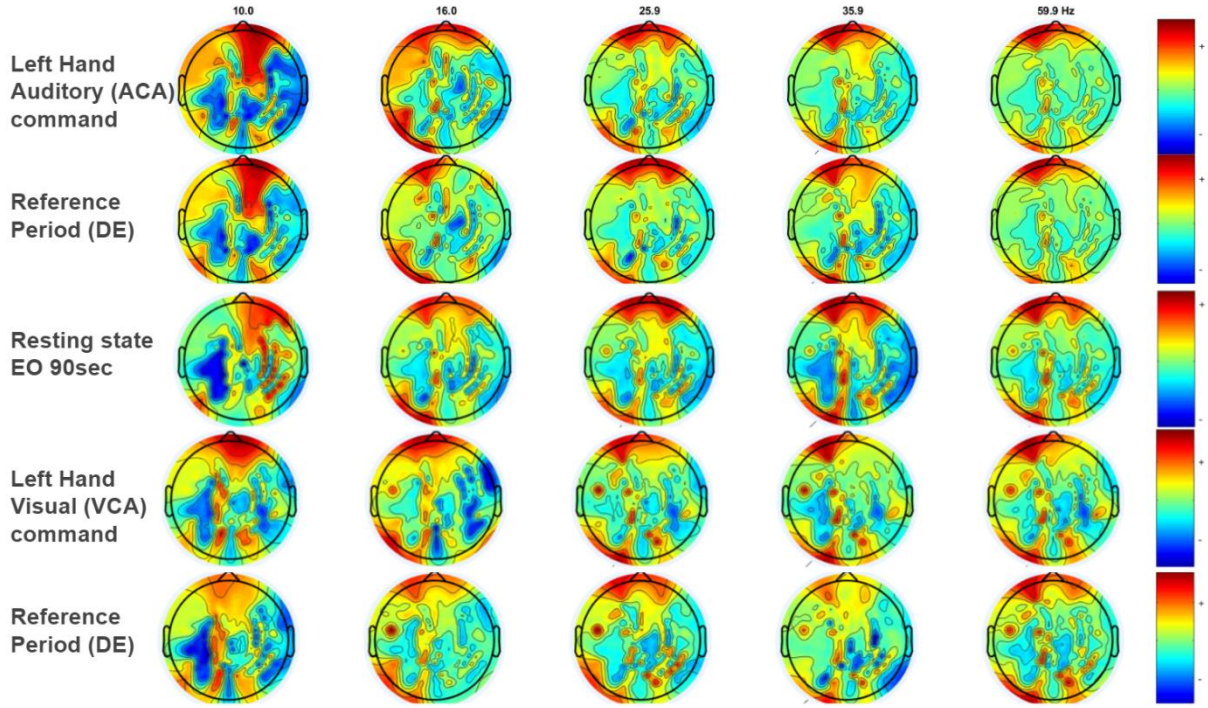


Figure 1-14 Auditory and visual motor task *Power spectral density of alpha, beta and gamma activity performed with the left hand. Data is shown for 500 ms epoch starting with hand reaction (MCA) (upper rows) and 1000ms reference period (NCA or DE). Recorded with dense array 256 channel EEG system, Ant Neuro, Netherlands. Copyright 2021 © Neurophysiology Plus Iceland https://sites.google.com/view/neurophysiologyplus E Ívarsson & OC Banea*

In March 2019, the auditory-motor task was completed with a ***visual-motor task*** in a single healthy participant. For the visual-motor task, we presented two commands, "press" and "no press", in a written form directly from a screen.

We looked to understand the gamma activity behavior we observed in the first subjects with the auditory stimuli. We hypothesized that the cortical fragmentation and "hand laterality" were not exclusively present due to auditory cortical activation (ACA) or motor cortical activation (MCA). Data were preprocessed together with Eysteinn Ívarsson (**Figure 1-14**). We presented this technique in Coimbra, Portugal (Eysteinn Ívarsson et al., 2019). Surprisingly, this was the first time when high-density 256 channel "bird-eye" view EEG mapping showed a difference in the reference period, we located between the command "press" and "no press". Higher power spectral density was observed during this "non-cortical activation" epoch (NCA), how we named it, in comparison with the epochs of auditory cortical activation (after the *11* and *12* codes for the commands "press" and "no press") and motor cortical activation (after the hand reaction button code *64*) (**Figure 1-15**).

[6] AVH-TMS Icelandic clinical trial lasted three years, between 2018-2021 and was organized by Reykjavík University, Department of Biomedical Engineering, Clinical Neurophysiology Unit of Neurology Department, National University Hospital of Iceland, and Icelandic Psychiatric Hospital Kleppur

[7] https://sites.google.com/view/schizophreniaplus

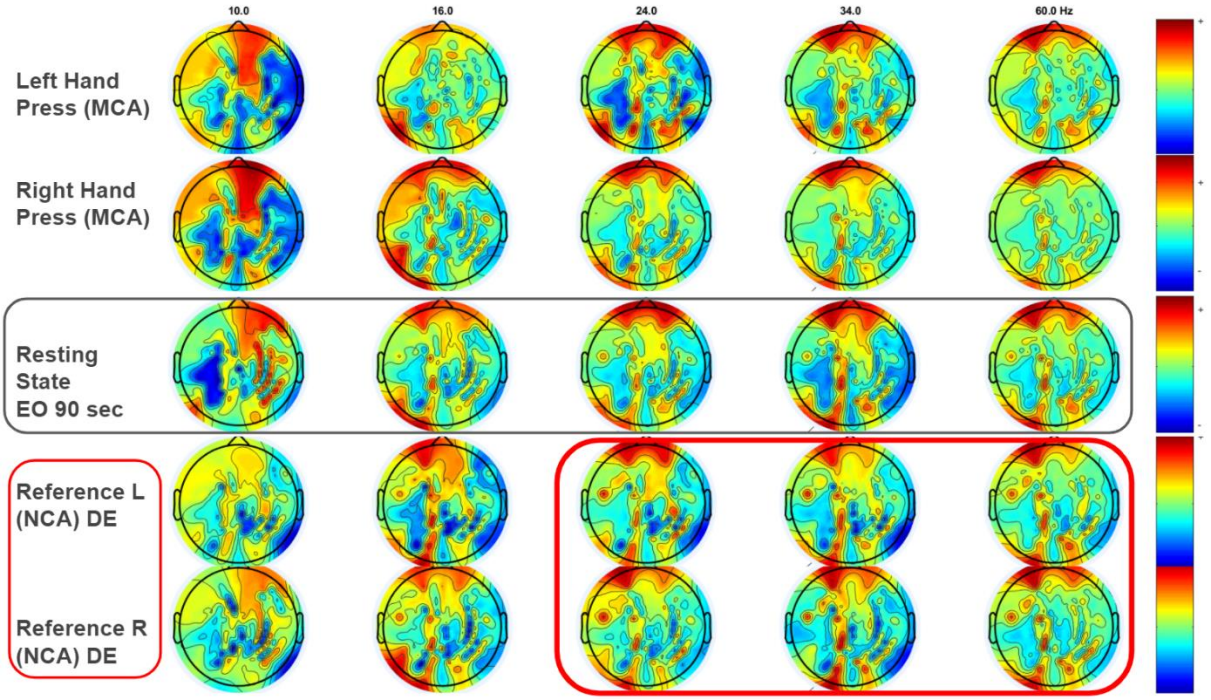


Figure 1-15 Auditory motor task *in a healthy participant. Power spectral density (bird-eye map) are shown for 10, 16, 25, 35, and 60Hz. DE=delayed epoch (Peled et al. 2001); ACA & VCA = epochs of 1000 ms after visual commands. Recorded with dense-array 256 channel EEG system, Ant Neuro, Netherlands. Copyright 2021 © Neurophysiology Plus Iceland https://sites.google.com/view/neurophysiologyplus E Ívarsson & OC Banea*

1.2.5 Silent period

i Cortical silent period

When TMS is delivered over the motor cortex while the subjects maintain voluntary muscle contraction, a pause in ongoing electromyography (EMG) activities follows the evoked motor response or compound motor action potential, which is called the silent period (Terao & Ugawa, 2002). At the cortical level, the cortical silent period (CSP) induced by TMS is an index of GABAB-mediated intracortical inhibition, which allows investigating motor inhibition within the primary motor cortex (M1) (Paci et al., 2021). A shorter CSP (poorer GABAB mediated cortical inhibition) is associated with more severe manic symptoms (Mehta et al., 2021), while an enhanced CSP duration was observed after ethanol acute consumption at euphoric / dis-concentration level (A. D. Jónasson, 2020; Turco et al., 2020; Ziemann et al., 1995). Diazepam, a benzodiazepine exerting its anxiolytic, anticonvulsant, muscle-relaxant and sedative-hypnotic properties by allosterically enhancing the action of GABA at GABAA receptors (Richter et al., 2012), shortened the duration of CSP probably by acting on subcortical structures (Inghilleri et al., 1996).

ii Cutaneous silent period

EMG inactivity from a voluntarily contracting muscle can also be induced peripherally, by an electrical stimulus applied to a cutaneous nerve (Caccia et al., 1973). This period of inactivity is named the cutaneous silent period (CuSP). The presence of a CuSP is dependent on intact small-diameter A-delta fibers, while the efferent reflex arm is formed by the large-diameter alpha motoneurons (Kofler & Poustka, 2004; Leis, 1998; Mota et al., 2015). A

minimal stimulus intensity of 40 mA and a minimal stimulus duration of 0.2 ms elicit maximal CuSP duration (J. Y. Kim et al., 2009). The precise physiologic mechanism by which inhibition occurs at a spinal level remains controversial. The CuSP may be a consequence of (1)

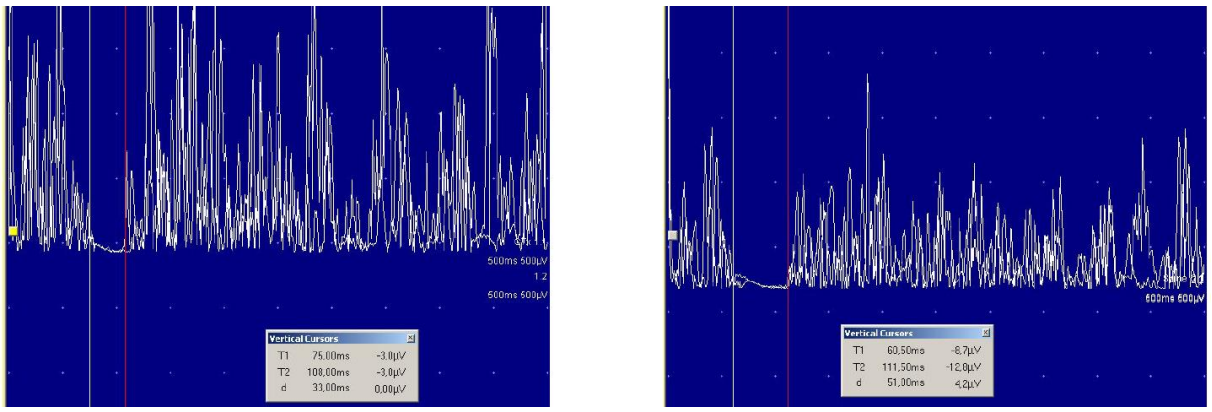


Figure 1-16 *The cutaneous silent period showed prolonged duration after 700 ml of acute ethanol intake. Y-axis division = 500 µV, X-axis division = 500 ms*

postsynaptic inhibition of spinal motoneurons; (2) pre- or post-synaptic inhibition of spinal interneurons that relay corticospinal impulses to the spinal motoneurons; (3) presynaptic inhibition of the direct corticospinal tract; or (4) a combination of these mechanisms (Leis, 1998). The contribution of the central nervous system to this peripheral cutaneous-muscular reflex is less investigated. The CuSP latency was significantly longer in patients with the pyramidal syndrome than in healthy subjects suggesting that corticospinal projections influence the CuSP latency probably by modulating the balance of excitability in the underlying circuits (Gilio et al., 2008). The duration of CuSP was longer in patients with Parkinson's disease, brachial dystonia, multiple system atrophy, after tramadol intake, 3 hours after administration of a single, 20 mg oral dose of the selective serotonin reuptake inhibitor, and 1 week after the initiation of pramipexole (0.5 mg/day). On the contrary, suppression of CuSP was observed during and shortly after vibration or in patients with restless leg syndrome (Gündüz et al., 2020). In previous work, we analyzed the effects of alcohol intake on CSP and CuSP in four healthy subjects and we observed an increment of CSP duration from 131.93 ms (SD 36.07) to 176.58 ms (SD 30.34) while CuSP showed an increased duration from 43 ms (9.76) to 51 ms (SD 10.23) (A. D. Jónasson, 2020). The change of CuSP duration after acute ethanol intake in one healthy subject is shown in **Figure 1-16**.

1.3 State of the art

Schizophrenia is characterized by delusions, hallucinations, disorganized speech and behavior, and other symptoms that cause social or occupational dysfunction (American Psychiatric Association, 2013) with patients experiencing abnormal language processing (Hirano et al., 2019) and cognitive deficits (Bowie & Harvey, 2006; Dickinson et al., 2013). Auditory verbal hallucinations (AVH) are a positive symptom of schizophrenia causing patients distress, functional disability, and risk to hurt themselves and/or others (Braham et al., 2004). Despite the progress achieved with antipsychotic medications, 25-30% of schizophrenia patients suffer from treatment-resistant hallucinations (Goghari et al., 2013; Meltzer, 1997; Shergill et al., 1998). Advances were done in the treatment of pharmaco-resistant AVH with cognitive-behavioral therapies (Jauhar et al., 2019), neurofeedback (Dyck et al., 2016; Rieger et al., 2016), or repetitive transcranial magnetic stimulation (RTMS) (Bais et al., 2017; Hoffman et al., 1999).

MLAE and sensory gating P50 suppression and P300 deficits in patients with schizophrenia were found to be of similar magnitude as findings reported in neuroimaging and neuropsychology (Bramon et al., 2004). N100 as a biomarker of neural plasticity (Gonzalez-Heydrich et al., 2016) together with P50, N100, and P200 sensory gating has been used to assess neuromodulation induced by low and high-frequency RTMS in healthy participants (Clement Nathou et al., 2015; Clément Nathou et al., 2018). Näätänen and Picton (1987) and Lijffijt et al. (2009) proposed that N100 gating may relate to filtering mechanisms involved in triggering attention while P200 gating may relate to the allocation of attention and the initial conscious awareness of a stimulus (Lijffijt et al., 2009; Näätänen & Picton, 1987). Studies have shown that patients with schizophrenia exhibit reduced N100 and P200, but similar P50 amplitudes, compared to controls (Rosburg et al., 2008; Schwarzkopf et al., 1995). It was found that sensory gating abnormalities in schizophrenia patients can be detected throughout the entire mid-latency range of information processing (50-400 ms) and are not limited to the pre-attentive stages (P50). Therefore, it was strongly suggested to assess N100 and P200 gating to this patient's category (Nashaat N Boutros et al., 2004). A meta-analysis of 29 studies using N100 sensory gating revealed no evidence for an auditory N100 gating deficit in schizophrenia, while N100 amplitudes to the initial stimulus (S1) showed significant differences, with smaller N100 in the patient group than in healthy controls. N100 amplitudes to the repeated click (S2) were widely similar for both patients and healthy controls (Rosburg, 2018). In a study of patients with schizophrenia, during AVH experience, P50, N100, and P200 were reduced indicating impaired sensory gating and this was correlated with hallucinations severity derived from PSYRATS (Thoma et al., 2017).

P50 and P300 topography While P300 topography in chronically ill schizophrenic and psychotic bipolar patients was associated with a specific left-lateralized posterior abnormality, suggesting underlying posterior temporal lobe dysfunction of a generator located in the left superior temporal gyrus (STG) (Morstyn et al., 1983; Salisbury et al., 1999), the scalp topography of P50 remains largely unknown (Kurthen et al., 2007) and has been less investigated.

EEG oscillations and connectivity Patients with schizophrenia have shown reductions of beta and gamma oscillations, and of synchronization during cognitive tasks and at rest, suggesting that there is an intrinsic deficit in the temporal coordination of distributed neural activity (Uhlhaas & Singer, 2010). Quantitative EEG (QEEG) was modified by psychotropic medications among patients with a schizophrenia spectrum disorder (Hyun et al., 2011; Ozaki et al., 2021). EEG studies showed that schizophrenia is associated with hyperconnectivity across different brain regions of multiple frequency bands (Di Lorenzo et al., 2015) and that aberrant gamma-band coupling between auditory cortices is related to the emergence of AVH (Steinmann et al., 2017). Gamma activity has been investigated in one of the following paradigms: (1) at rest, (2) during "bottom-up" sensory stimulation, or (3) "top-down" cognitively driven tasks. Pre-stimulus baseline gamma activity was elevated, and task-driven 'evoked' gamma-band responses were reduced in schizophrenia (Gandal et al., 2012). During an auditory cued motor task schizophrenia patient, especially those with severe auditory hallucinations, had reduced gamma-band response directly preceding the motor response (Ford, 2016; Ford et al., 2007). It was suggested that the auditory, language, and memory cortical networks are significantly disturbed, and interconnected neural oscillation deficits in these networks during processing or perception of speech underlie the pathophysiology of schizophrenia (Ford, 2016).

Graph theory and network organization Graph theory was used to study functional and effective connectivity using functional magnetic resonance imaging (fMRI) in patients with schizophrenia (Xiang et al., 2020) and with dense-array 128 channel EEG in patients with major depressive disorder (Sun et al., 2019). In patients with chronic pain, acceptance and

commitment therapy (ACT) reduced the connectivity in the pain network (including left putamen, right insula, left insula, and right thalamus) as revealed by graph theory obtained from resting-state fMRI (Young et al., 2014a). Repetitive transcranial magnetic stimulation aftereffects were assessed with graph-theoretical metrics in patients with depression (Olejarczyk et al., 2021). Graph using network topology structure elements like clustering coefficient or node betweenness centrality had the ability to discriminate major depressive disorder (MDD) patients from normal controls, which indicated that these network metrics might be served as the electrophysiological characteristics for probable MDD identification (Sun et al., 2019). Using brain network analysis including degree, betweenness centrality, nodal clustering coefficient, local efficiency, and participation coefficient in a study on 71 schizophrenic patients and 74 healthy controls researchers could identify the patients with schizophrenia with an accuracy of 93.1 % (Xiang et al., 2020).

Cortical and cutaneous silent period Transcranial magnetic stimulation (TMS) may also be a potential method by which sensory processing can be assessed since TMS paradigms like the cortical silent period (CSP) can be used to measure GABAB-mediated cortical inhibition that is linked with sensory gating. The patients with schizophrenia showed prolonged CSP, and this had a positive correlation with an increased symptom score of the positive and negative symptom scale (Tang et al., 2014). Another study showed that clozapine-treated persons with schizophrenia had significantly longer CSP compared with healthy subjects and unmedicated persons with schizophrenia, suggesting a deficit of cortical inhibition in persons with unmedicated disease related to the severity of psychotic symptoms (Daskalakis et al., 2008). In patients with first-episode schizophrenia, risperidone showed an increment of CSP at four weeks, suggesting an association between risperidone monotherapy and an increase in GABAB mediated inhibitory neurotransmission (Ustohal et al., 2016). Significant prolongation of the cortical silent period (CSP) was also observed after three weeks of treatment with quetiapine (Frank et al., 2014). Regarding the cutaneous silent period (CuSP), little is known on how the corticospinal tract and central inhibitory mechanisms affect the peripheral cutaneous-muscular reflex, and if this neurophysiological test can be used in patients with schizophrenia.

RTMS treatment and schizophrenia Non-invasive brain stimulation techniques like repetitive transcranial magnetic stimulation (RTMS) have been proposed to disrupt mechanisms of AVH in patients with treatment-resistant schizophrenia. Several meta-analyses found moderate to high effect size for the AVH treatment with low-frequency 1Hz RTMS applied over left temporoparietal junction (T3-P3 EEG location) (Aleman et al., 2007; J.-P. Lefaucheur et al., 2014; Slotema et al., 2014; Sommer et al., 2012). Most of these studies investigated the effects of RTMS in treatment-resistant patients as an ad-on or second-line treatment using as outcomes psychometric scores. A more recent meta-analysis including eleven randomized controlled studies was unable to definitively support or refute the routine use of 1-Hz RTMS in treating AVH in clinical practice (J. Li et al., 2020). At the moment of writing this dissertation, there is only one study[8] in which RTMS at 1Hz was applied in patients with the first episode of psychosis and without antipsychotic drugs (NCT03544333, 2018). The RTMS was delivered in four sessions with 1000 pulses (1Hz) applied within one day. The results available for four patients (two with real T3-P3 treatment and two with sham treatment) showed increased Hallucination Change Score in the patients of the treatment group, while control patients remained with stable scores.

[8] Boost RTMS for AVH - Therapeutic Response and Neurobiological Prediction Markers in AVH

1.4 Document structure

The 2nd Chapter of this thesis includes the aim, the research questions, subjects' characteristics, and the protocol design of the AVH-TMS study[9]. The 3rd Chapter, named "*Exploratory works*" includes the pilot studies of this thesis. In *Study 1* is described the methodology used to obtain P50 and P300 responses. In *Study 2*, we attempted to use a simple method of auditory-motor task with the exploratory objective to trigger beta and gamma activity, hypothesizing that patients with schizophrenia elicit more power spectral density (PSD) and relative power of beta and gamma activity during a cognitively-driven task compared with the resting state. In *Study 3*, we explored cortical and cutaneous silent period as neurophysiological markers of inhibitory system. The 4th Chapter contains three *hypotheses-generating* studies. In *Study 4*, we looked to investigate the "triggered attention" and "sensory gating" responses after RTMS. We proposed a method of sampling the signal from 7 regions of interest and we measured N100 and P200 obtained with the paired-click paradigm. Further, *Study 5* was focused on P300 responses and here we analyzed time, frequency domains, and connectivity with participation coefficient. In *Study 6*, we assessed changes induced by RTMS to the brain functional connectivity by analyzing data of the auditory-motor task with graph theory and small-worldness (**Figure 1-17**). The 5th Chapter contains a critical view on the neurophysiological concepts described in this thesis and the strengths of this work. After the Bibliography, in the Appendix, three original articles and two oral communications are reprinted following the journal reprint policies.

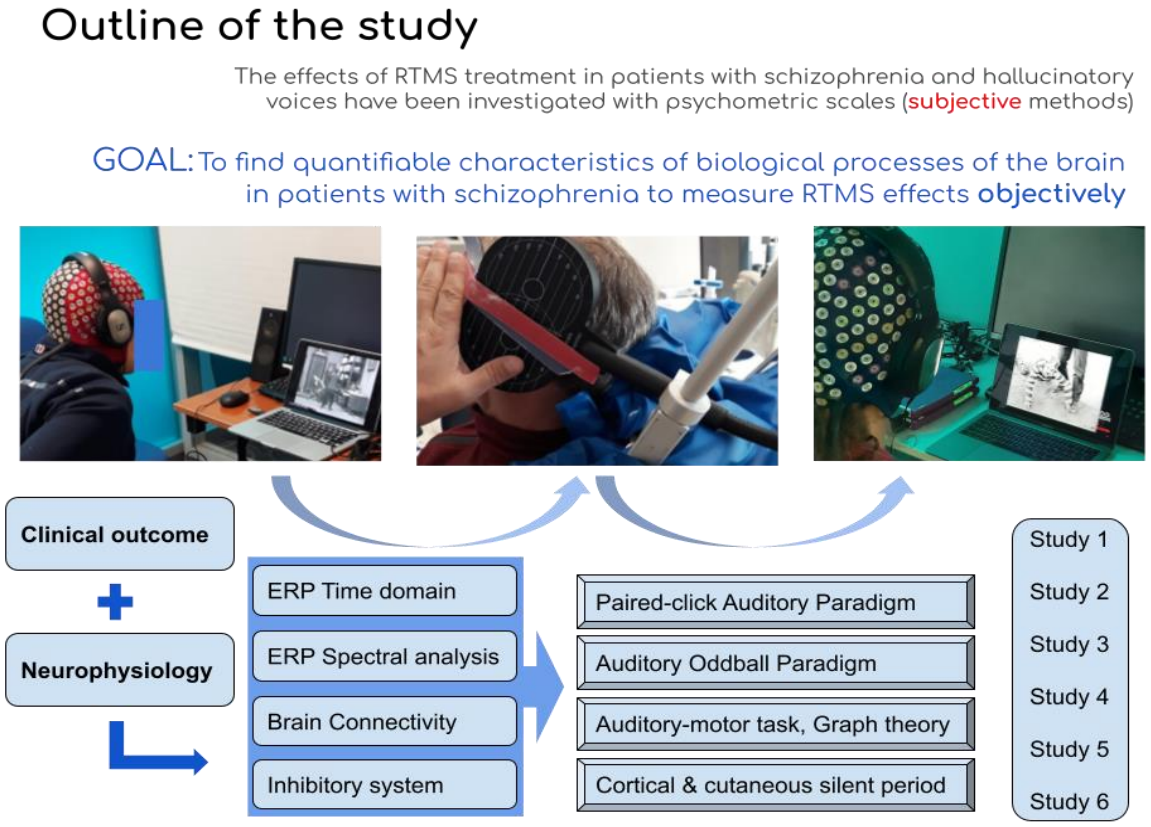


Figure 1-17 *Outline of the study*

[9] AVH-TMS Icelandic clinical trial lasted three years, between 2018-2021 and was organized by Reykjavík University, Department of Biomedical Engineering, Clinical Neurophysiology Unit of Neurology Department, National University Hospital of Iceland, and Icelandic Psychiatric Hospital Kleppur

This dissertation is original work by the author, Ovidiu C. Banea. Much of the thesis is based on the original articles and publications, of which I, Ovidiu C. Banea, am an author. A list of all works related to the AVH-TMS Icelandic clinical trial is available online[10]. All works were presented in conferences or congresses during the period of my doctoral studies. Here are cited five of the most relevant works. Three original articles were published in peer review journals (Articles i, iv, and v).

i. Marcu S, Pegolo E, Ívarsson E, Jónasson AD, Jónasson VD, Aubonnet R, Gargiulo P and OC Banea (2020). Using high-density EEG to assess TMS treatment in patients with schizophrenia. *European Journal of Translational Myology*, 30(1), 134-138. https://doi.org/10.4081/ejtm.2019.8903

ii. Banea OC, Pegolo E, Marcu S, Friðriksdóttir R, Ívarsson E, Jónasson AD, Jónasson VD, Magnusdóttir BB, Haraldsson M, Wassermann E and P Gargiulo (2020). P50 and P300 Event-Related Potentials in Patients with Schizophrenia Recorded from High-Density EEG. In: Henriques J., Neves N., de Carvalho P. (eds) XV Mediterranean Conference on Medical and Biological Engineering and Computing – MEDICON 2019. MEDICON 2019. *IFMBE Proceedings*, vol 76. Springer, Cham. Reprint license Nr 5174381122461, Oct 2021 https://doi.org/10.1007/978-3-030-31635-8_130

iii. Ívarsson E, Shaw A, Georgsdóttir AÓ, Magnúsdóttir BB, Jónasson AD, Wassermann E, Gargiulo P, Stefansson SB, and OC Banea (2020). A Novel Technique to Trigger High Beta and Low Gamma Activity in Patients with Schizophrenia. In: Henriques J., Neves N., de Carvalho P. (eds) XV Mediterranean Conference on Medical and Biological Engineering and Computing – MEDICON 2019. MEDICON 2019. *IFMBE Proceedings*, vol 76. Springer, Cham. Reprint license Nr 5174381445355, Oct 2021 https://doi.org/10.1007/978-3-030-31635-8_129

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[10] https://sites.google.com/view/schizophreniaplus/publications-news

2 Chapter. The Present Investigation

2.1 Study aim

The aim of this work was to determine the degree to which repetitive transcranial magnetic stimulation (RTMS) is effective for the treatment of patients with schizophrenia and persistent auditory verbal hallucinations (AVH).

Exploratory objectives were to determine if the symptoms of patients with schizophrenia change after intervention with 10 days of low-frequency 1Hz RTMS and to explore if neurophysiological tests like quantifying auditory event-related responses (P50 suppression, N100-P300 complex), EEG (electroencephalography) relative power, functional connectivity, and the cortical silent period (CSP) show changes after the RTMS treatment.

2.2 Research questions

Exploratory Study 1. Sensory gating is impaired in patients with schizophrenia (Adler et al., 1985; Olincy et al., 2010) and P300 showed decreased amplitude in patients when compared to healthy controls (Turetsky et al., 2015). Where the P50 suppression and P300 waves show major changes or dysfunction at cortical level remain unclear as most studies reported P300 data at Pz and Cz electrodes and P50 researchers consistently reported analysis at Cz and thus only this location was used for analysis (Bramon et al., 2004). We looked mostly to reproduce paired-click, and oddball auditory paradigms in healthy controls and patients with schizophrenia and to develop a quantitative method of ERP with dense-array 256 channel EEG.

Exploratory Study 2. It has been suggested that schizophrenic symptoms can be explained by over-arousal causing depression in neural activity or inverted-U relationship between performance and arousal, the also called Yerkes-Dodson Law (Grossberg, 2000; Yerkes & Dodson, 1908). Our study followed this suggestion and we expected that in schizophrenia the high-beta and gamma activity will break up in clusters and decrease during a task requiring attention, whereas in normal subjects these bands activity will be increased. A cognitively driven auditory-motor task was suggested as "triggering beta and gamma neural synchrony" in the cortical regions involved in the working memory and auditory-motor cortices.

Exploratory Study 3. Results pertaining to CSP in schizophrenia patients are controversial. Prolonged CSP was observed among both first-episode patients and clozapine medicated chronic patients compared with healthy controls, suggesting alterations within the GABAB-mediated neurotransmitter system (Daskalakis et al., 2002). One study found no significant differences in CSP between SCZ patients and healthy controls, and others have reported a shortened CSP in either the chronic or unmedicated patients (Fitzgerald et al., 2002; S.-K. Liu et al., 2009). Based on these findings, the working hypothesis was that CSP will be prolonged after RTMS as a signal of improvement in the inhibitory system related to sensory gating. Additionally, we looked to cutaneous silent period, which was expected to be prolonged, too. Both data are presented as case studies.

Study 4. We expected that RTMS would reduce AVH severity (hypothesis H1), that stress and anxiety would be reduced, and that quality of life would be increased after the RTMS (hypothesis H2). Based on the assumption that there is impaired triggering of attention in patients with schizophrenia, as made evident by reduced N100 amplitude (Rosburg et al., 2008)

we expected that N100 amplitude would be higher after the RTMS (hypothesis H3) and that N100 and P200 sensory gating which appeared to be impaired in patients with schizophrenia and AVH will improve (hypothesis H4).

Study 5. In this study, we looked at the N100-P300 complex voltage before and after the treatment expecting that after the treatment the amplitude of P300 will be higher in patients receiving RTMS at T3-P3 EEG location. PSD has been performed from the event-related oscillations and we looked to the network organization and the difference between T2 (post-TMS) and T1 (pre-TMS) conditions. Network organization was analyzed with participation coefficient, a metric of functional segregation. The question was if P300 related oscillations and local connectivity participation index derived from a dense-array 256 channel EEG system can be considered as candidates for biomarkers of the patients with schizophrenia.

Study 6. EEG measures, including spectral density and evoked potentials, have been used as measures of the physiological response to TMS treatment. The PSD changes observed in response to attentional demands can be of interest to monitor patients with schizophrenia behavior (Barr et al., 2011). Following our observations that the cortical distribution of the relative power in different EEG bands showed topographical EEG fragmentation the question was if there will be increasing values of the relative power after the RTMS, especially for beta and gamma bands. Auditory-motor task results were compared with the resting state. Later, it would be of extreme importance to evaluate if there are congruent changes in brain connectivity. We expected that network organization measured with the graph theory and small worldness will show an improved small world effect.

2.3 Subjects

Ten patients with schizophrenia aged between 26 and 48 (seven men and three women, mean age 32.4, SD = 6.85) and six healthy control subjects aged between 24 and 43 (four men and two women, mean age 30.3, SD = 7.5) participated in the studies. Three other patients were excluded from the study prior to RTMS treatment (**Table 1**). The patients were recruited from the National University Hospital of Iceland psychiatric inpatient service and outpatient clinics. Patients were eligible for inclusion if they were between 18-55 years of age and had treatment resistant AVH for at least 1 year. Treatment-resistant AVH was defined as a lack of clinically meaningful response to two trials of pharmacotherapy at the recommended dosage, lasting at least 6 weeks. Exclusion criteria included the history of epilepsy, daily cannabis use, or the use of other illegal drugs within one month prior to the study or during the study, drinking more than three units of alcohol daily, or having any contraindication during the pretreatment interview (Rossi et al., 2011). The patients were taking one or more antipsychotic medications. Healthy subjects were Reykjavik University students, exchange students, or Clinical Neurophysiology Unit employees. Two patients and two healthy participants were left-handed on the Edinburgh handedness inventory (Oldfield, 1971).

Table 1 *Characteristics of the Enrolled Patients: TG = T3-P3 RTMS, CG = Cz RTMS, marked patients abandoned the study.*

Treatment Group, left temporoparietal (T3-P3) RTMS				
Patient	Gender	Age (M; SD)	Medication	Diagnostic
S15TG	m	48	Clozapine, Amisulpiride, Propranolol and Clonazepam	Paranoid Schizophrenia
S16TG	m	35	Clozapine, Fluoxetine, Bupropion and Metformin	Paranoid Schizophrenia
S17TG	m	30	Clozapine, Olanzapine, Perphenazine, Alprazolam, Levomepromazine, Oxazepam and Melatonin	Paranoid Schizophrenia

S18TG	f	33	Sertraline, Quetiapine, Pregabalin and Zopiclone	Schizoaffective disorder
S19TG	m	30	Clozapine and Flupenthixol	Paranoid Schizophrenia
S20TG	m	30	No pharmacological treatment	Paranoid Schizophrenia
S21TG	f	31	Perphenazine, Olanzapine, Escitalopram	Unspecified psychosis
	5 m 2 f	34; 6,51		
Control Group, vertex (Cz) RTMS				
S22CG	m	26	Clozapine, Pregabalin, Amisulpiride	Hebephrenic Schizophrenia
S23CG	f	30	Aripiprazole, Olanzapine, Chlorprothixene and Pregabalin	Paranoid Schizophrenia
S24CG	m	27	Clozapine, Olanzapine, Bupropion and Propranolol	Paranoid Schizophrenia
S25CG	m	26	Paliperidone, Quetiapine, and Perphenazine	Paranoid Schizophrenia
S26CG	f	39	Clozapine, Flupenthixol, Zopiclone, Mirtazapine, Escitalopram, Metformin, Metoprolol and Chlorpromazine	Paranoid Schizophrenia
S27CG	f	50	Zuclopenthixol, Alprazolam	Paranoid Schizophrenia
	3 m 3 f	33; 9,67		

2.4 Study protocol

All study patients, care providers, and psychologists were blinded to treatment group assignment except the neurotechnicians who set up the proper coil location. Patients agreeing to take part in the study were first administered psychometric scales and then had EEG recorded with five blocks paired-click paradigm, P300 oddball paradigm, and auditory-motor task (T1). The order of the tasks was randomized.

TG and CG patients were invited to return for identical psychometric scores interviews, ERPs recordings, and auditory-motor task analyses within one week after the RTMS treatment (T2) (**Figure 2-1**). The third group of six healthy subjects (HS) with no RTMS treatment served as a comparison for the auditory evoked responses and auditory-motor task of patients' groups. All HS were submitted to a Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1997) to ensure that they were in good mental health conditions. The study was approved by the Ethics Committee of the National University Hospital of Iceland (Approval No 21. 2018).

The procedures and all the risks were explained to all participants and all questions were answered, after which, they gave written informed consent regarding their participation. Patients were given 10.000 ISK (80 EUR) for their participation and offered to take a pre-paid taxi to and from the hospital or university where the treatment and EEG analyses were performed.

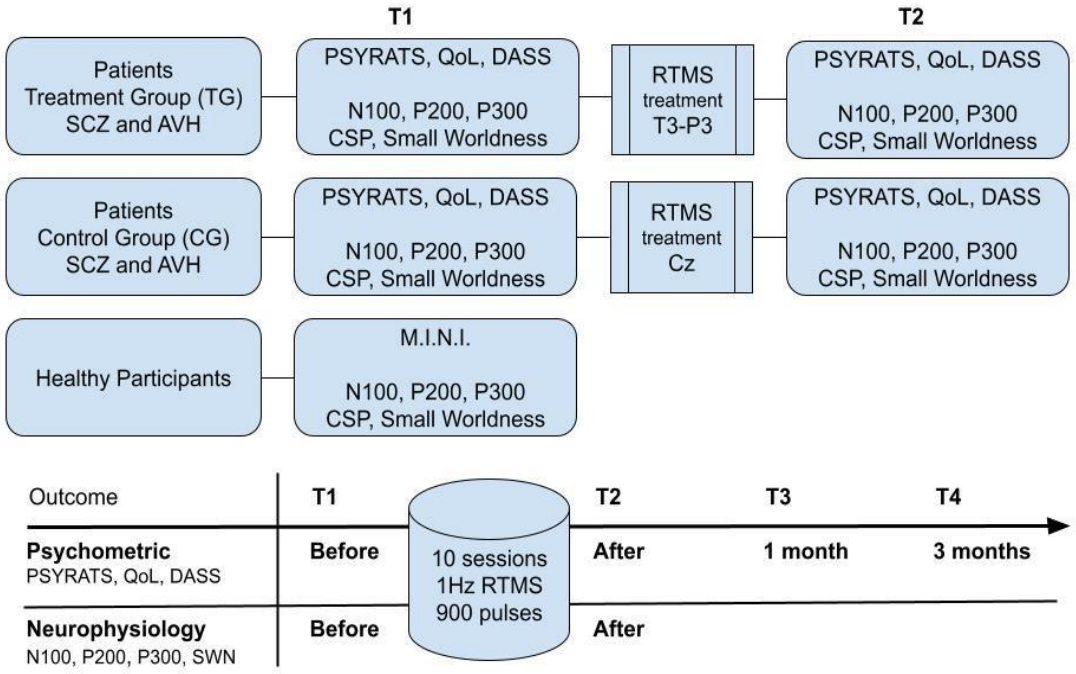


Figure 2-1 *Study and protocol design*

2.5 Psychometric scales

Quality of Life (QoL)

Quality of Life (QoL) is a 16 item self-report scale consisting of five conceptual domains of quality of life: material and physical well-being, relationships with other people, social community and civic activities, personal development, and fulfillment, and recreation. The scale maximum score is 112 and has been shown to have good test-retest reliability and good convergent and discriminant validity (Flanagan, 1978).

Depression Anxiety Stress Scales (DASS)

DASS is a measure of mental health focusing on three traits of depression, anxiety, and stress. The list consists of 42 items, rated on a four-point Likert type scale of how much that symptom occurred in the last week. In clinical samples, the scale maximum score is 126 and has shown excellent internal consistency and temporal stability as well as excellent discriminant validity and good convergent validity (Brown et al., 1997).

Psychotic Symptom Rating Scales (PSYRATS)

The score of the PSYRATS auditory hallucinations subscale (AHS) is represented by a structured interview that measures auditory hallucinations (11 items) rated on a five-point ordinal scale (0-4). The maximum score of AHS is 44. The scale measures the severity of AVH for the past week on eleven dimensions which are: frequency, duration, location, loudness, beliefs about origin, negative content, the intensity of negative content, amount of distress, the

intensity of distress, disruption of life, and control. PSYRATS has shown excellent inter-rater reliability and good discriminant and convergent validity for both chronic and first-episode psychosis (Drake et al., 2007; Haddock et al., 1999).

2.6 Neurophysiological tests

i. EEG recordings in three conditions: Resting-state (RS), auditory-motor task with the left hand (AMT-l), auditory-motor task with the right hand (AMT-r)
ii. Auditory paired-click paradigm (**Figure 2-2**)
iii. Oddball auditory paradigm
iv. Cortical silent period
v. Cutaneous silent period

Figure 2-2 *During the paired-click paradigm, the patients looked to a silent film to avoid drowsiness.*

2.7 RTMS treatment

A Medtronic MagPro stimulator TMS device and a figure-of-eight coil (MC-B70) were used. The resting motor threshold (RMT) was defined as the lowest intensity producing an MEP of 50 μV, peak-to-peak, in five out of ten trials in relaxed *abductor pollicis brevis* (APB) muscle (Daskalakis et al., 2008). Stimulation was delivered at 100% of the APB resting motor evoked potential threshold, determined before each treatment session. The treatment consisted of ten consecutive sessions over two weeks with an interval at the weekend. Each RTMS session lasted 15 minutes and included 900 pulses at a frequency of 1 Hz. The RTMS was delivered with the same parameters at the left temporoparietal region for TG (T3-P3 EEG location) and at the vertex (Cz EEG location) for CG.

3 Chapter. Exploratory works

3.1 **Exploratory Study 1.** Using high-density EEG to assess TMS treatment in patients with schizophrenia (Marcu et al., 2020)

Deficits in sensory gating are an important endophenotype for schizophrenia (Toyomaki et al., 2015) and P300 was suggested as a robust marker of both positive symptoms and decreased cognitive and functional capacity in patients with this chronic (Turetsky et al., 2015). This study presents a new technique of quantifying P50 and P300 auditory evoked potentials recorded from different scalp regions using 256 dense array EEG.

3.1.1 Methods

Paired-click paradigm

The paired-click paradigm was performed to elicit the P50 component. A pure tone (1500 Hz, 6-ms duration at comfortable hearing noise) was used as the click sound and presented during a 500-ms interval through headphones. We presented 150 paired stimuli in 5 blocks with an inter-pair interval of 10 seconds, which provided 25 minutes of EEG measurement (Light et al., 2010). In consideration of participant load and ear comfort that could influence EEG measurement, we instructed participants to watch a silent film and presented auditory stimuli from headphones as mentioned above. The S1 response was identified as the most prominent peak in the 40 to 80 ms post-stimulus windows. The preceding negative trough was used to calculate the S1 amplitude. For the S2 response, the positive peak with latency closest to that of the S1 peak was selected. P50 suppression was calculated as the ratio of the mean value of the S2 amplitude to the mean value of the S1 amplitude (S2:S1) (Hall et al., 2011; Olincy et al., 2010; Van Luijtelaar, 2003). The difference of S1 minus S2 amplitude was also used as a comparison.

Oddball auditory paradigm

N100-P300 complex. In our study P300 response was measured with an auditory oddball paradigm attention task. The recordings were carried out between 11:00 and 14:00 hours. The subjects were sitting in a comfortable chair with their eyes closed. The frequent (F) and the rare (R) auditory stimuli were presented binaurally through headphones at an interstimulus interval between tones of constant 1.1 sec. For each subject, there was 1 trial of 160 tones which occurred randomly with a probability of 0.2 (Stefánsson & Jónsdóttir, 1996).

We instructed the participants to pay attention to the rare stimuli without counting or moving a finger. The rationality of this was to do not activate additionally the precentral gyrus or parietal lobe during the complementary auditory-motor task and frequency-domain studies.

EEG preprocessing and analysis

The EEG was recorded using a 256-channel system (ANT Neuro, Netherlands[11]) with an electrooculogram (EOG) electrode placed below the right eye, and a ground electrode placed on the left side of the neck. Data pre-processing and analysis were performed with Brainstorm (Tadel et al., 2011) and MATLAB 2018b. The data were sampled at 1024 Hz and re-referenced to the average of left and right mastoid electrodes (R19R, L19L). A bandpass filter was set between 0.1-80 Hz and a notch filter from 49-51 Hz was used to remove undesired monomorphic artifacts from 50 Hz mains electricity. Bad channels were removed when EEG voltage was greater than ±80 μV; if more than 10% of the channels showed too much noise or bad signal, the whole trial was rejected. For P50 analysis the signals were digitized for an epoch of 500 ms starting 100 ms prior to the presentation of each auditory stimulus (-100 ms to +400 ms) and for P300 response analysis the signals were digitized for each epoch of 1000 ms starting 100 ms prior to the presentation of each auditory stimulus (-100 to +900 ms). Baseline correction was performed using a pre-stimulus 100 ms window and "bad "channels were removed and interpolated. Individual trials were visually inspected and rejected when indicative of excessive muscle activity, eye movements, or other artifacts (see Chapter 5, Discussions).

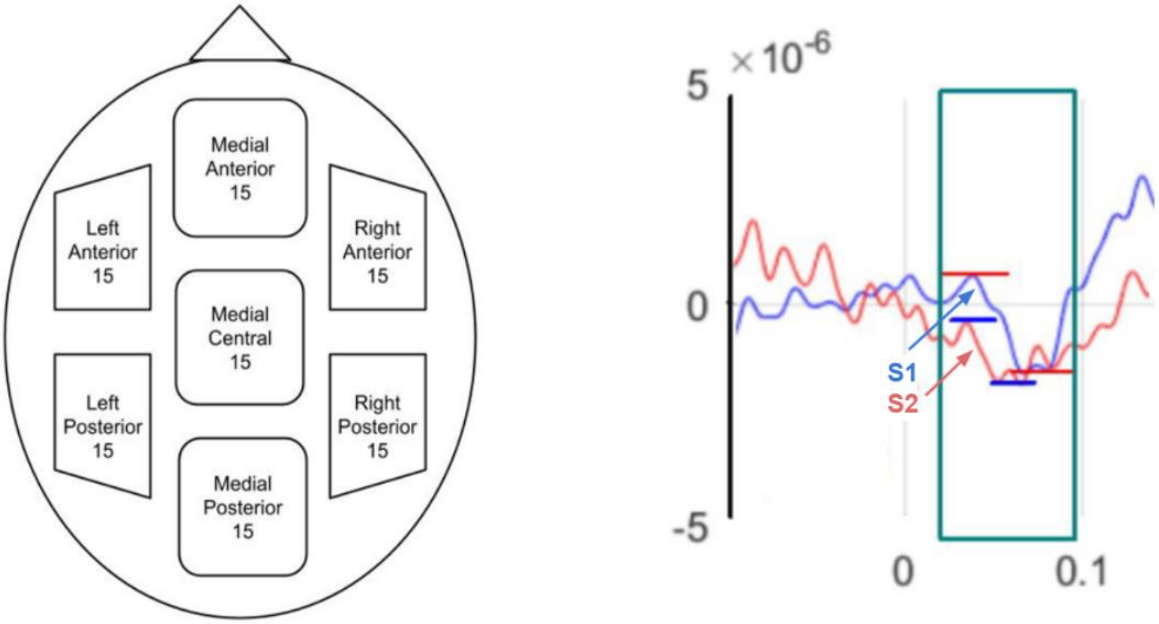


Figure 3-1 *The regions of interest employed in Study 1 and Study 4. S1 is the response to conditioning stimulus and S2 is the response to testing stimulus. The 0 to 0.1 segment on X-axis corresponds to 100 ms.*

The Regions of Interest

The regions of interest (ROI) were defined using a MATLAB script as follow: Left Anterior (LA), Left Posterior (LP), Medial Anterior (MA), Medial Central (MC), Medial Posterior (MP), Right Anterior (RA) and Right Posterior (RP) (**Figure 3-1**). Fifteen electrodes were selected from 3 parallel lines for each region (105 electrodes). We measured the peak-to-peak P50 amplitude from a preceding negative trough to the positive peak at 30-70 ms range from the stimulus onset (**Figure 3-1**). N100-P300 complex values for each ROI were calculated as the difference between the most negative voltage value and the most positive voltage value within the time range of 80-500 ms. In this work, the P50 suppression ratio and N1-P3 wave's signals were represented as the average of the fifteen channels of every ROI.

[11] https://www.ant-neuro.com

3.1.2 Results

Recording event-related potentials with a high-density EEG system is challenging and difficult. Data recorded from two patients and two healthy participants showed major P50 suppression (reduced ratio) in healthy participants (**Figure 3-2**) compared with P50 suppression of both patients. The patients showed higher ratios on the left anterior and left posterior regions

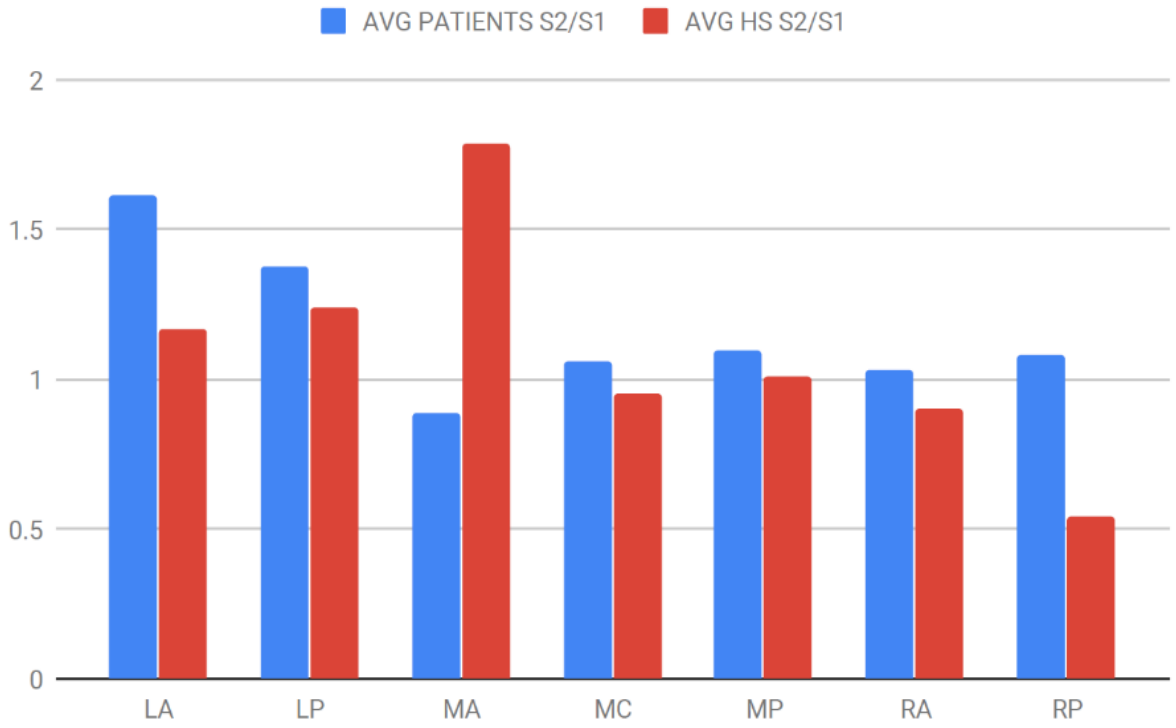


Figure 3-2 *The P50 gating in two patients with schizophrenia (T1) and two HS. Ratio method S2:S1*

suggesting that these regions might be functionally affected or that gating in healthy participants is higher on the left anterior and left temporoparietal region.

Healthy participants showed better responses over the right posterior or temporoparietal region (lower value of S2:S1 ratio). S1-S2 P50 amplitude difference (method) showed similar results with more gating in patients over left anterior and left posterior regions (**Figure 3-3**).

N100-P300 components were obtained and visible in the healthy group. Data from one patient with schizophrenia showed reduced or absent deviant stimulus responses before the treatment (T1), which changed and was more visible after the treatment (T2). After three months we could observe a reduced amplitude of the N1-P3 complex. Even so, the automatic maximum-minimum voltage measurements for 15 electrodes in each ROI detected higher responses in the patient's group on a few occasions which at visual inspection resulted to be erroneous due to original signal difficulty acquisition or data processing.

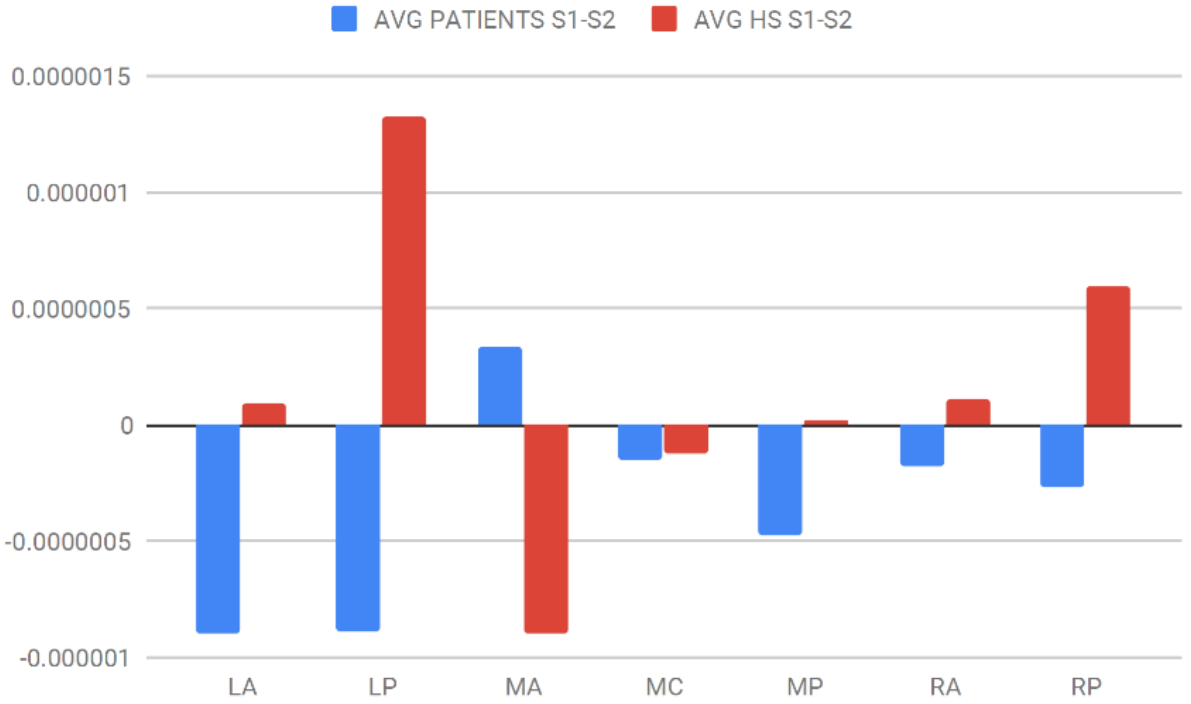


Figure 3-3 *The P50 gating in two patients with schizophrenia (T1) and two HS. Difference method S2-S1*

P50 examples

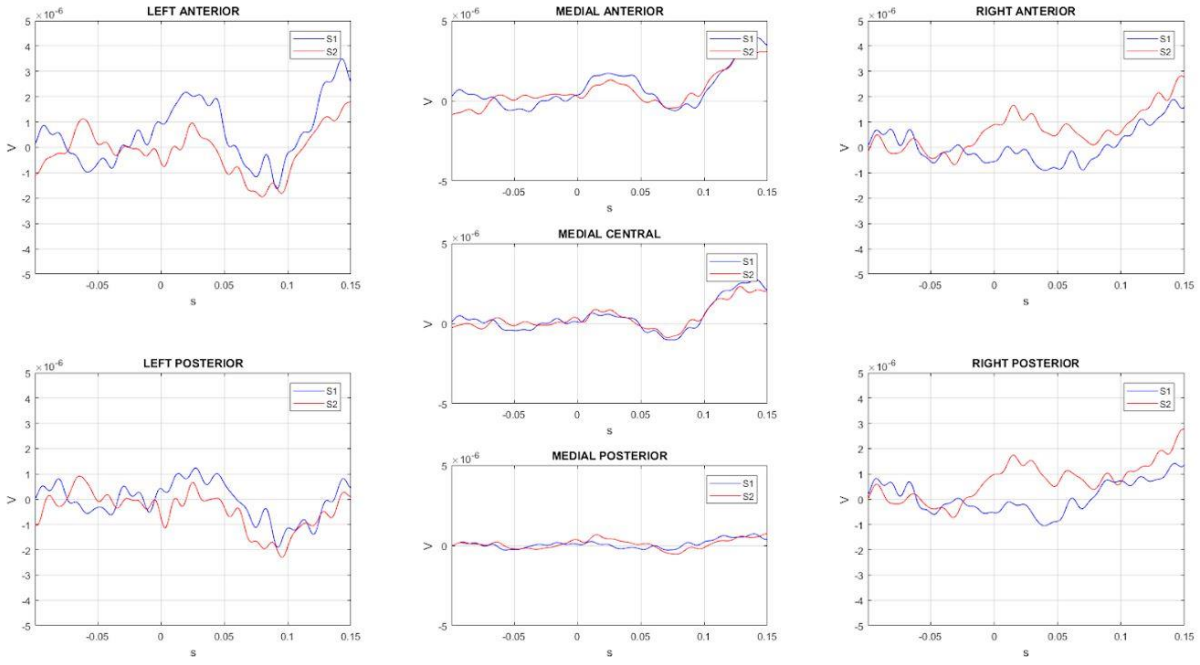


Figure 3-4 *P50 topography in a patient with schizophrenia and AVH after RTMS (T2). The gating of P50 is visible at both anterior and temporoparietal regions.*

N100-P300 complex

N100-P300 complex was measurable for all selected regions and it appears to be a helpful neurophysiological marker in assessing if ERPs components change after RTMS treatment at the stimulation site or in other different cortical areas.

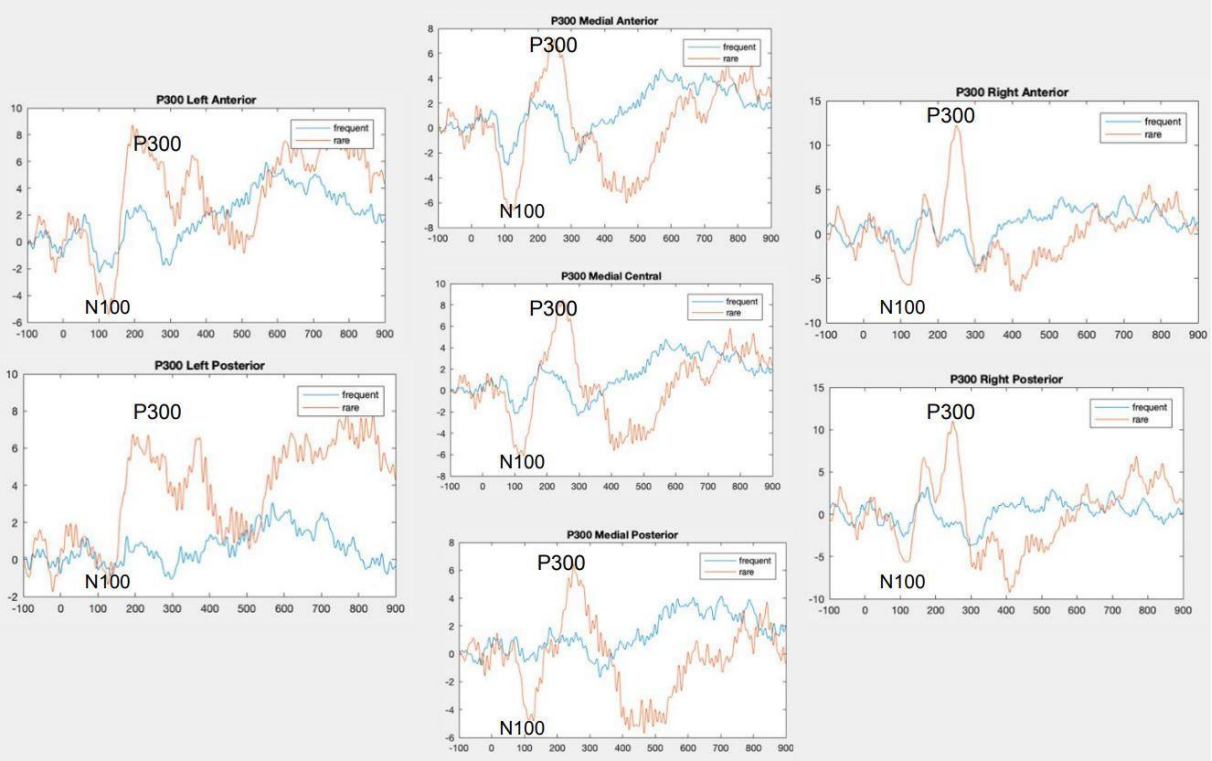


Figure 3-6 *N100-P300a complex in a healthy participant.*

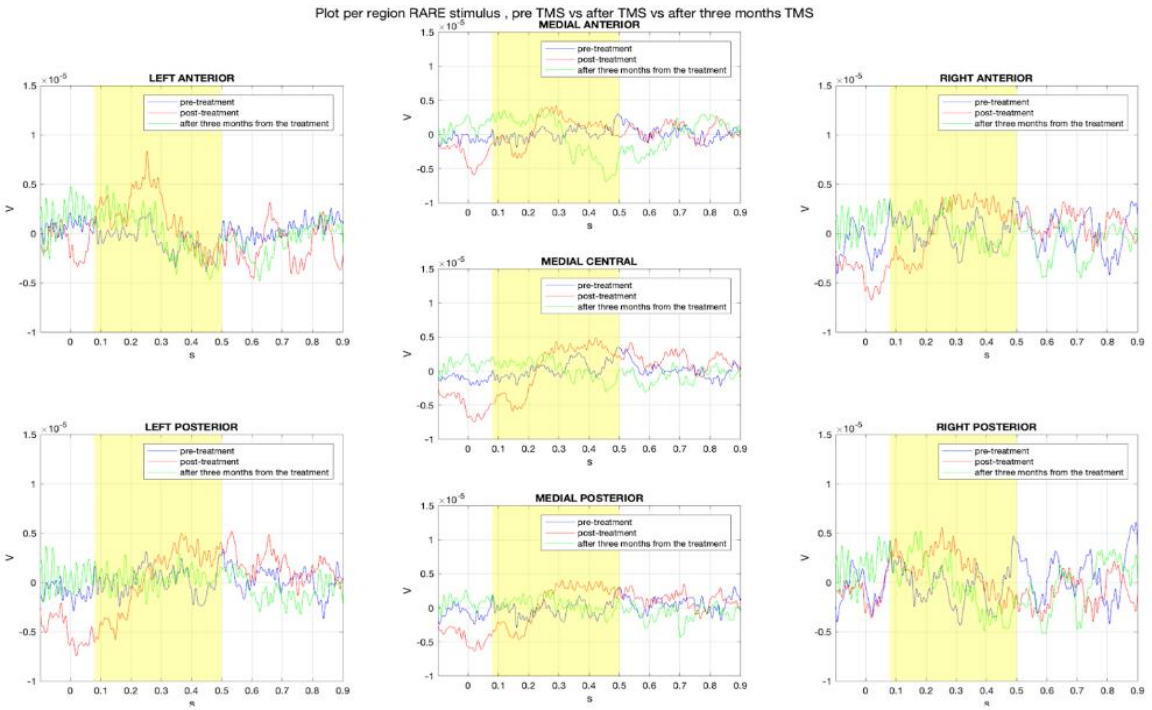


Figure 3-5 *N100-P300 complex in a patient with schizophrenia and AVH before (blue), within one week after RTMS (red), and after three months from the treatment (green).*

At baseline, healthy subjects showed N100-P300 complex topography with higher values at left and right anterior regions which are located over the frontal lobes, and midline (MA and MC regions), while the patients with SCZ showed higher voltage over left and right anterior and posterior regions and less amplitude from the midline (**Figure 3-7**).

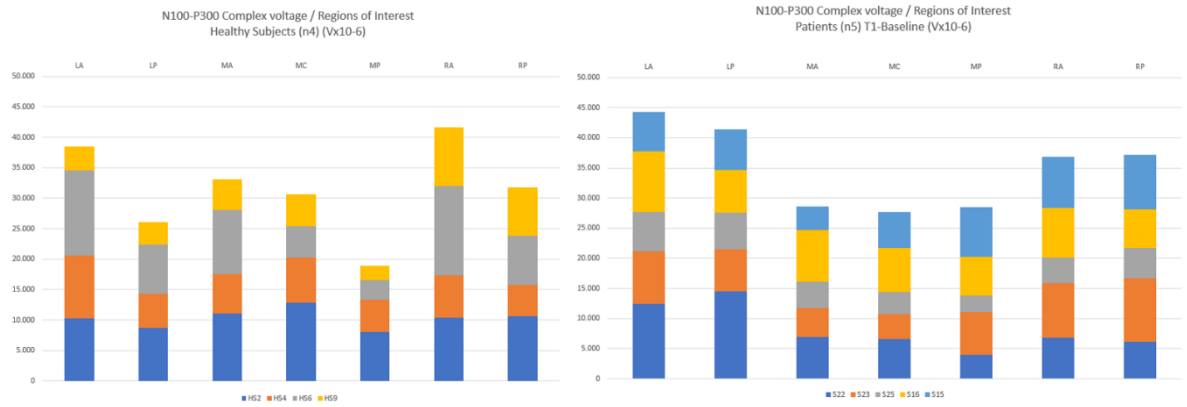


Figure 3-7 *Topography of N100-P300 complex in four healthy subjects (left) and in five patients with schizophrenia and AVH before the treatment (T1). ROI from the left to the right: Left Anterior (LA), Left Posterior (LP), Medial Anterior (MA), Medial Central (MC), Medial Posterior (MP), Right Anterior (RA) and Right Posterior (RP).*

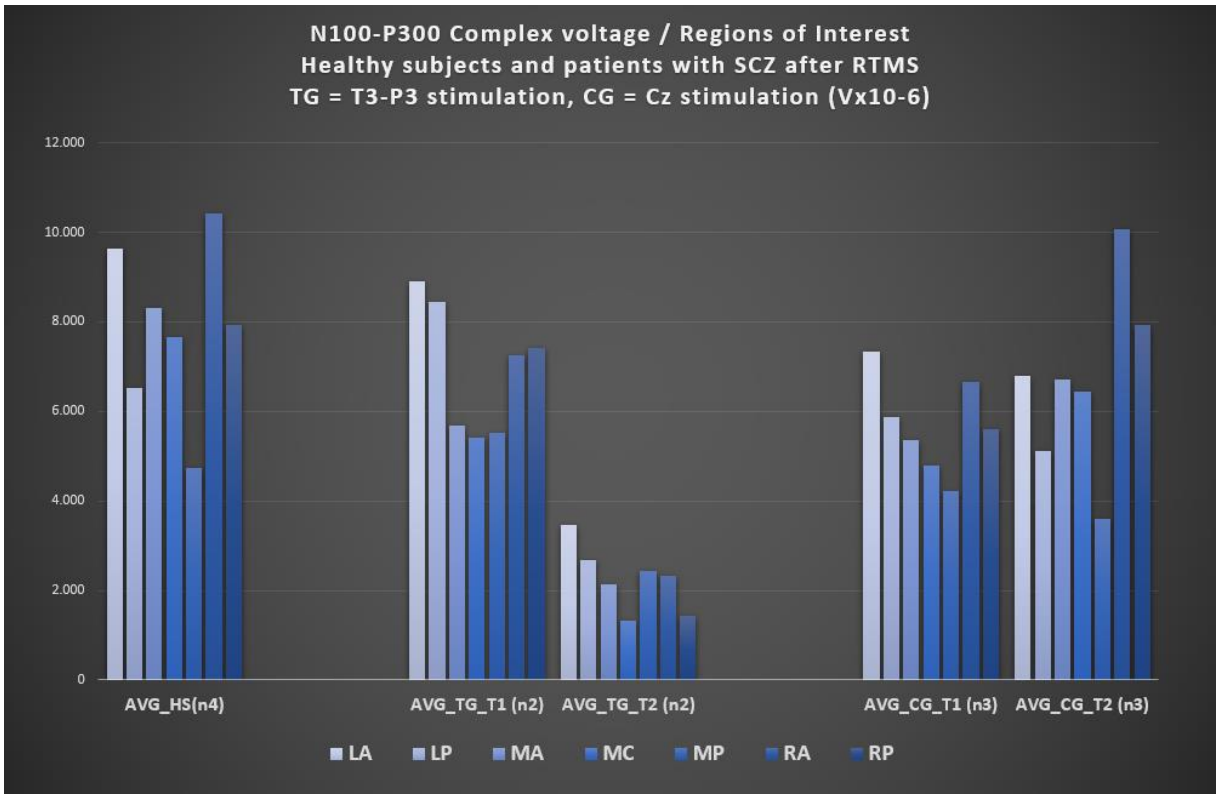


Figure 3-8 *N100-P300 complex topography in 4 HS and 5 Patients with SCZ in T1 and T2 (after RTMS).*

After RTMS, all patients (TG + CG, N=5) showed reduced N100-P300 complex voltage at the mid posterior (MP) region, with TG patients (N=2) showing the major global difference with reduced voltages in all regions (**Figure 3-8**). Individual data showed reduced P300 amplitude in all patients after RTMS treatment, with the S15 subject showing no values after RTMS in MP region (**Figure 3-9**). P300 was elicited with passive task conditions in which the subject did not respond to either the standard or target stimuli (Polich & McIsaac, 1994). These

results are in contrast with our hypothesis.

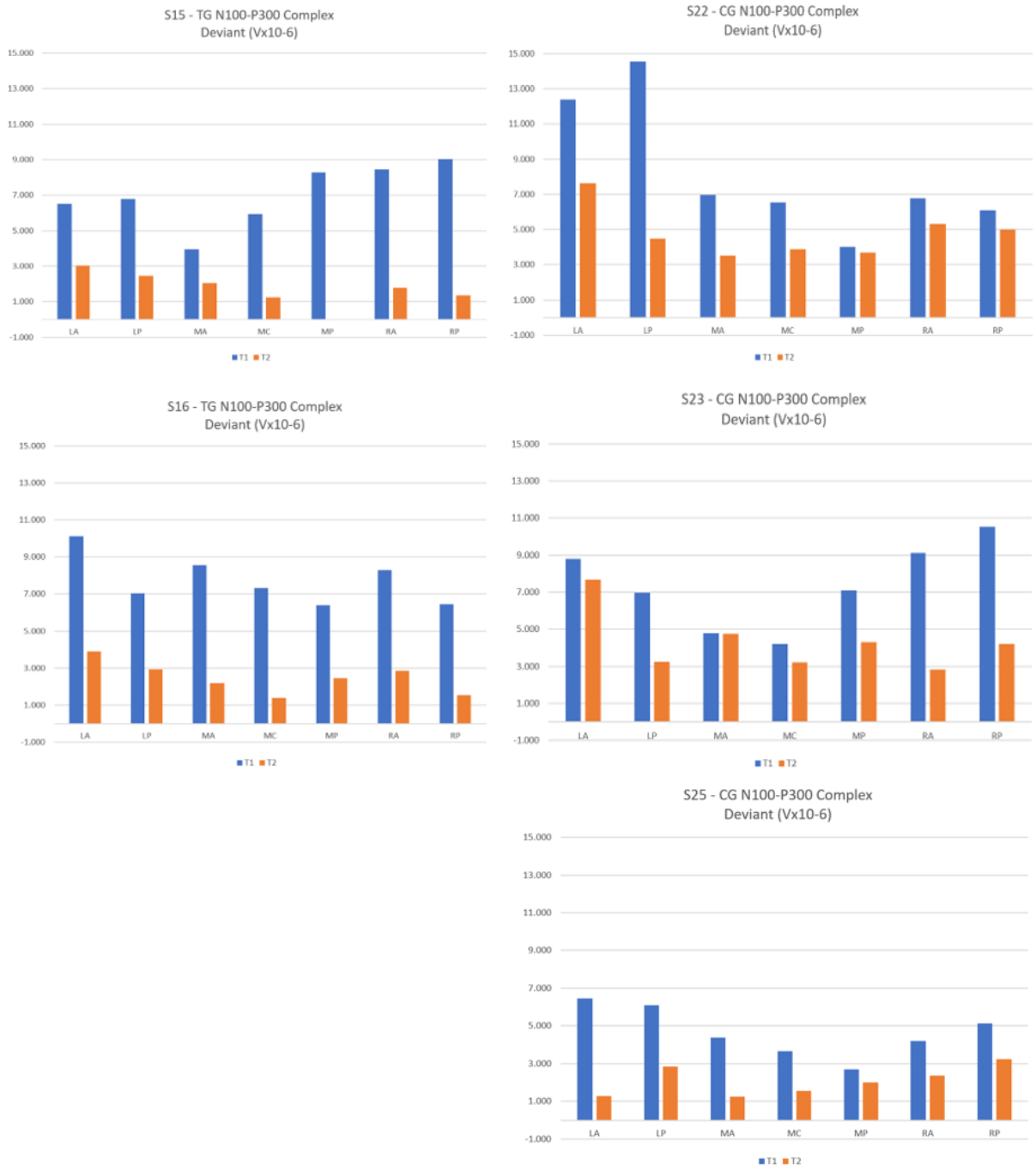


Figure 3-9 *Individual data of N100-P300 topography in patients with schizophrenia and AVH before (T1-blue) and after 10 days of RTMS (T2-orange). On the left are represented two TG patients and, on the right, three CG patients.*

3.2 **Exploratory Study 2.** A Novel Technique to Trigger High Beta and Low Gamma Activity in Patients with Schizophrenia (E. Ívarsson et al., 2020)

3.2.1 Methods

The auditory-motor task (AMT) was employed in a sound-attenuated room, and each patient was awake, un-sedated, and comfortably seated on a chair during the tasks. Subjects held a button in one hand and placed the hand on the thigh. We instructed each subject to press the button using the thumb when the pre-recorded verbal command "press" was given and not to press the button when the verbal command "no press" was given fig. Subsequently, each subject completed two auditory-motor tasks (one for each hand). The AMT task contained 40 trials: 20 auditory verbal "press" commands and 20 "no press" commands. The interstimulus interval was 3 seconds (Nagasawa et al., 2010). The commands were presented in a pseudorandom sequence during each task. The AMT was performed with the dominant hand (AMT-r), and non-dominant hand (AMT-l) one time in HC and two times in the patients (SCZ), before the RTMS treatment (SCZ-T1) and within one week after completing ten sessions of RTMS treatment (SCZ-T2).

EEG recording and preprocessing

The EEG was recorded using a high-density 256 channel ANT Neuro (Netherlands) system with an electrooculogram (EOG) electrode placed below the right eye, and a ground electrode placed on the left side of the neck. The EEG was recorded at a sampling rate of 1024 Hz. The raw EEG was exported and analyzed using the EEGLAB toolbox (v14.2.2) in MATLAB 2018b. EEG signals were first notch filtered at 50 Hz, and a later band-pass filter was applied between 0.1 and 80 Hz (Hall et al., 2011). Eye movements and muscle artifacts were removed by visual inspection. Bad channels were identified by automatic detection using kurtosis, or spectrum measures and later interpolated using the spherical method. The length of the resulting resting-state pre-processed data was 40 sec ± 10 sec for each participant. Finally, the remaining artifact-free continuous data were analyzed.

Data analysis

First, we analyzed 40 ± 10 sec resting-state EEG with eyes closed for three patients with schizophrenia and we compared it with the EEG of three healthy control participants. For the auditory-motor task, epochs related to the cognitively driven "motor cortical activation" (MCA) were segmented between -500 ms to +500 ms (1000 ms) relative to the onset of the button code (hand reaction) seen in the EEG trace. The reference period was set between +1500 ms to +2500 ms post-verbal command or auditory stimulus onset (1000 ms). Finally, the remaining artifact-free trials were analyzed. Here are presented the results of motor cortical activation (MCA) for one HS and one patient with auditory verbal hallucinations (AVH), using power spectral density (PSD) and topographical frequency maps including both hands sensory-motor regions. Later, ACA, MCA, and NCA epochs were modified (***Study 6***) to avoid overlapping of the EEG data (**Figure 3-10**). We looked at specific frequencies related to the motor reaction: low beta (13–20 Hz), high beta (20–30 Hz), low gamma (30–45 Hz), and high gamma (45-80 Hz). The brain maps showed topographical changes on specific frequencies: 16, 25, 35, and 65 Hz. We

compared data with the reference period and with the resting state EEG.

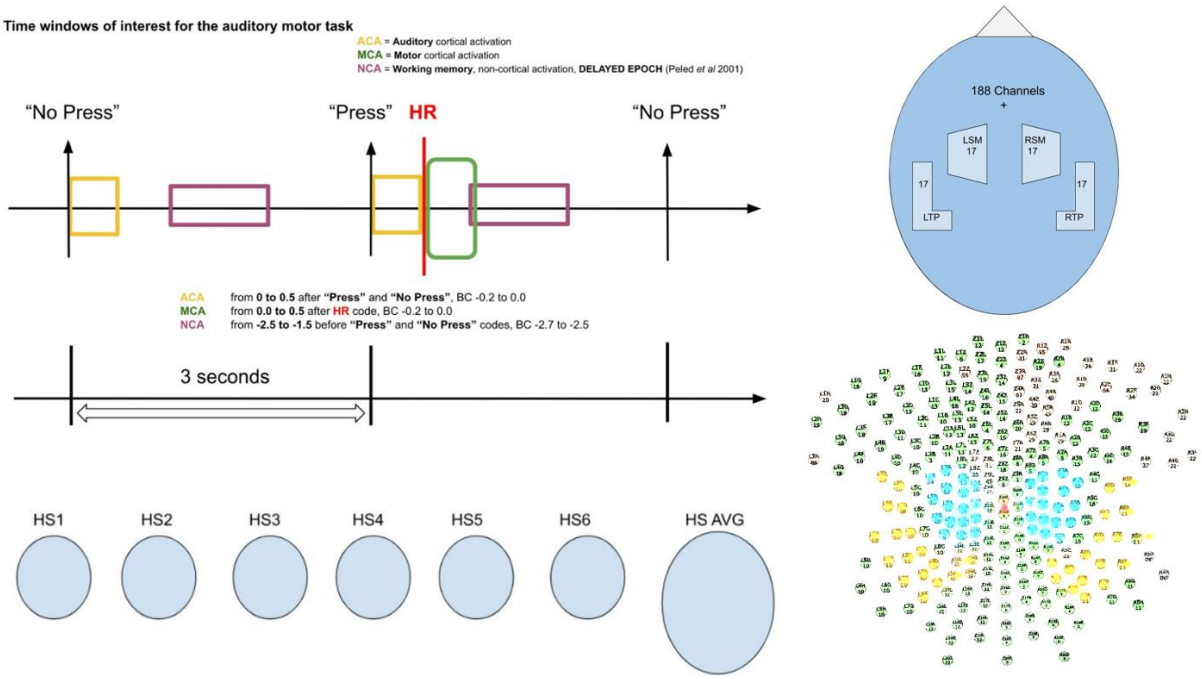


Figure 3-10 *AMT windows of interest (top left): ACA from 0-500 ms after "Press" and "No press", MCA from 0-500 ms after the Hand Reaction code, NCA or Delay Epoch from -2500 to -1500 ms before "Press" and "No Press" codes. ROI (bottom right): left and right sensorimotor regions (blue) and left and right auditory temporoparietal regions (yellow).*

3.2.2 Results

Healthy subjects

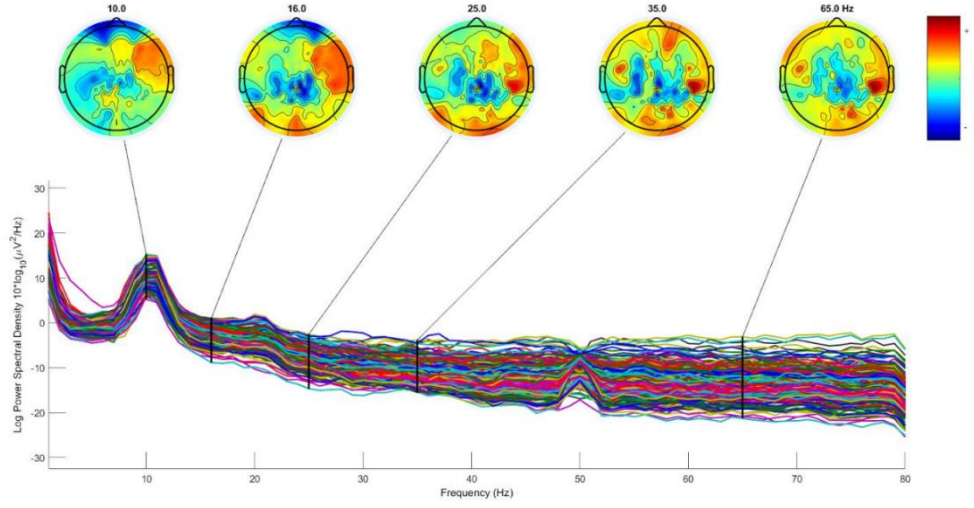


Figure 3-11 *PSD and "bird-eye" view EEG maps for three HS. Resting state, eyes closed.*

Patients

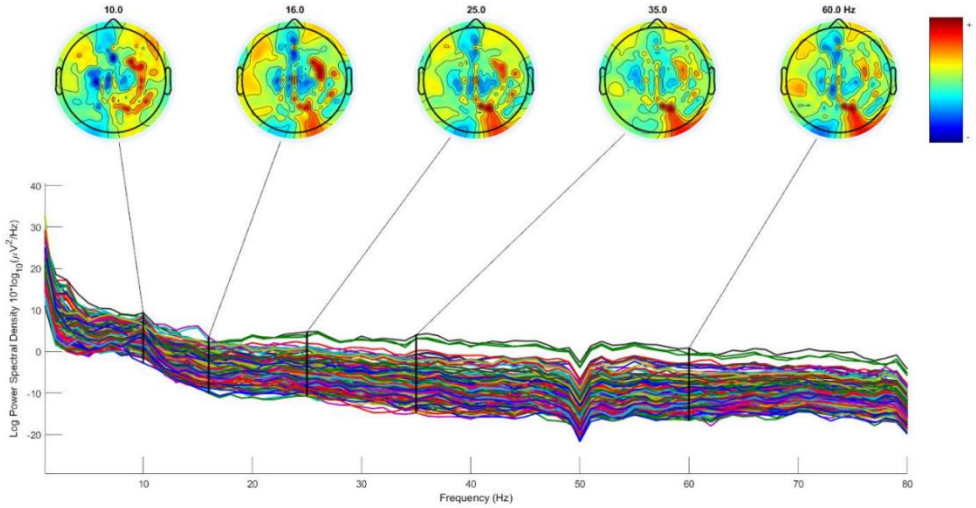


Figure 3-12 *PSD and "bird-eye" view EEG maps for three patients with SCZ and AVH. Resting state, eyes closed.*

The aim of this experiment (E. Ívarsson et al., 2020) was to investigate whether there are differences in cortical activity between healthy subjects and patients with schizophrenia during resting state and during an auditory-motor task. Furthermore, we wanted to investigate if the auditory-motor task would modulate beta and gamma activity. Our hypotheses were that: 1) The resting-state EEG shows differences of cortical activity in beta and gamma frequencies between healthy control participants and patients with schizophrenia, being more clustered in schizophrenia patients and 2) The auditory-motor task would reduce beta and gamma cortical distribution, compared to the RS in SCZ patient when compare it with the HC participant.

The results appeared to be congruent with our hypotheses, showing more clustered and fragmented cortical distribution in patients with schizophrenia (**Figure 3-11**, **Figure 3-12**) and reduced activity during the auditory-motor task, even during the reference period between the auditory commands. The activity seems to be stable during the task, with little lateralization effect of hand response.

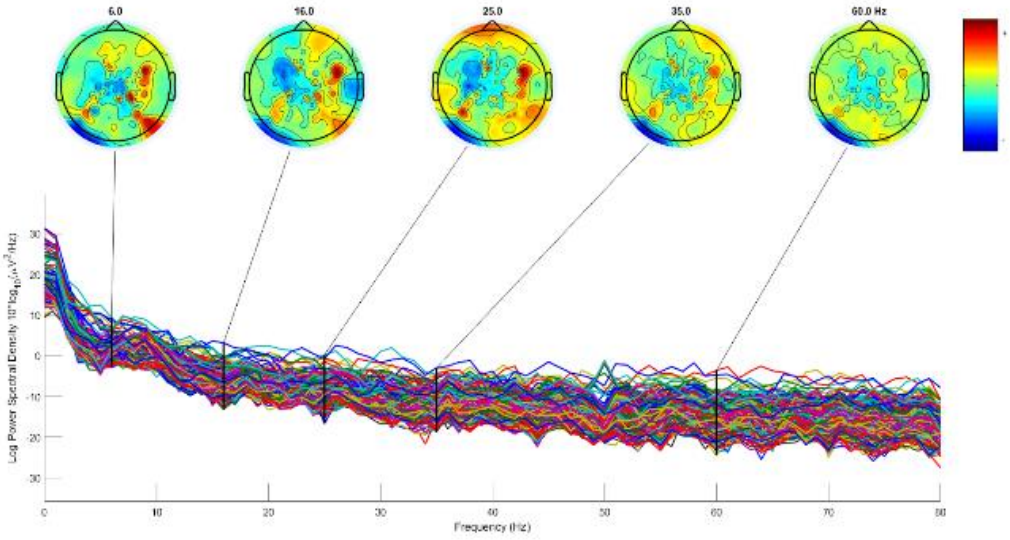


Figure 3-13 *Motor cortical activation during the AMT in a patient with schizophrenia (S15) in baseline condition T1. The task is performed with the left hand.*

3.3 **Exploratory Study 3.** The cortical and cutaneous silent period in patients with schizophrenia and AVH

In this work, we looked to CSP as a measure of central GABAB-mediated cortical inhibition that is linked with sensory gating and to CuSP which is a peripherally spinal cutaneous-muscular reflex that seems to be modulated also from the central corticospinal tract or intracortical inhibitory neurons. We expected that RTMS treatment might influence CSP and CuSP in patients with schizophrenia and pharmaco-resistant auditory verbal hallucinations by enhancing the total duration.

3.3.1 Methods

The cortical silent period (CSP) duration was measured in sub-maximally contracted *abductor pollicis brevis* muscle by stimulating the motor cortex using TMS with an intensity of 140% resting motor threshold (RMT). RMT has been classically defined as the amount of transcranial magnetic stimulation (TMS) machine output (intensity) necessary to produce a motor-evoked potential (MEP) that exceeds a defined peak-to-peak amplitude (usually 50 μV) 50% of the time in a finite number of trials (Borckardt et al., 2006). Calculations of CSP were determined from the motor evoked potential (MEP) onset to the recovery of any voluntary EMG activity. Three to five trials were repeated to obtain the average CSP duration for each subject (**Figure 3-14**). To obtain cutaneous silent period (CuSP) electrical stimuli were delivered to the ipsilateral dermatome of the 2nd digit from the dominant hand. Stimuli were delivered with ring electrodes at 10 times x sensory threshold. Surface EMG electrodes recorded CuSP from *abductor pollicis brevis* muscle while the patient was requested to continuously sustain a submaximal contraction. When the stimulus produced a clear and visible silent period, three trials were collected for each subject.

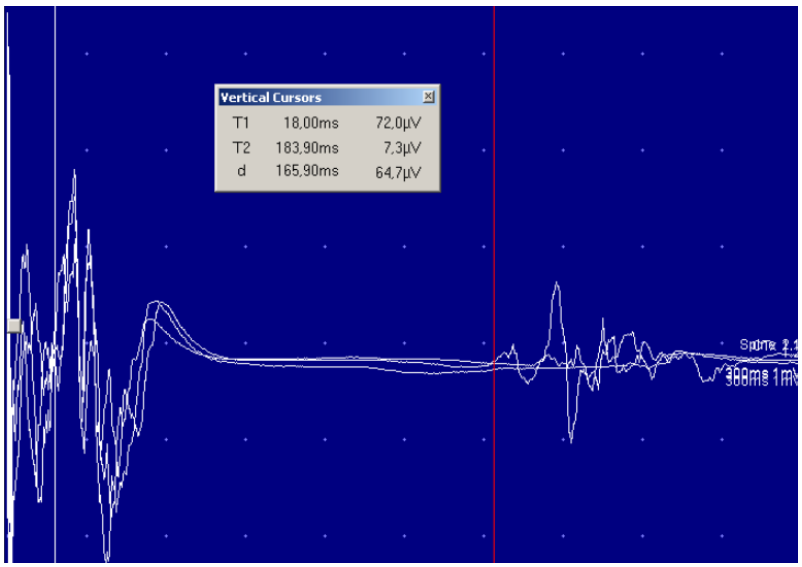


Figure 3-14 *Cortical silent period (TMS).*

Subjects In this work participated five patients from the TG (mean age 34.8, SD 7.7, one female), six patients from the CG (mean age 33, SD 9.7, three females), and six HC (mean age 28.5, SD 5.4, one female). CSP and CuSP were measured before treatment (T1), within one

week after the RTMS (T2), one month after RTMS (T3), and three months after RTMS (T4) (Table 2). Descriptive analysis is presented for both groups.

3.3.2 Results

CSP in the baseline condition (T1) had a duration of 161.33 ms (SD 19.87) in the HC group, 137.25 ms (SD 19.35) in TG, and 167.33 ms (SD 67.93) in CG. After the RTMS, the cortical silent period increased or decreased in patients from both groups (**Figure 3-15**) suggesting that this marker is difficult to interpret in patients taking many drugs and having difficult therapeutic management (Table 1).

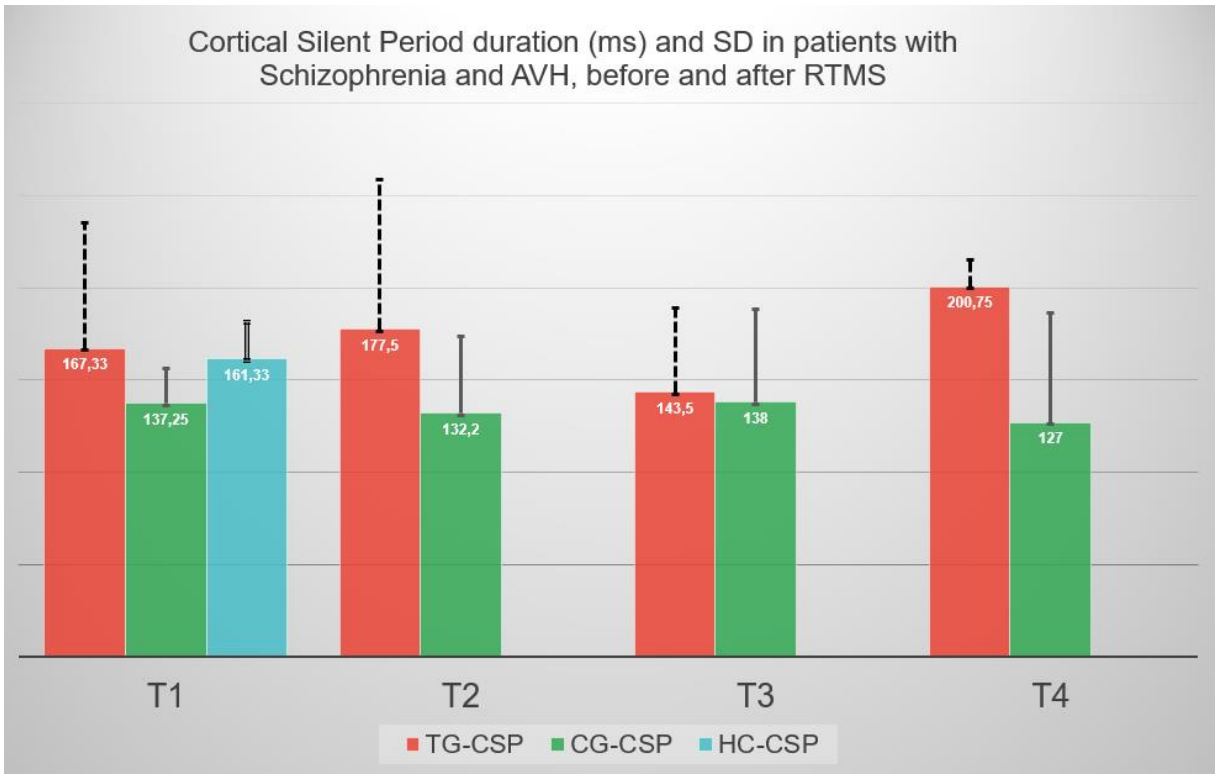


Figure 3-15 *CSP in patients with schizophrenia before (T1), after (T2), 1 month after (T3) and 3 months after (T4) RTMS*

At baseline, the cutaneous silent period showed a similar duration in all analyzed groups (TG, GC, and HC). After RTMS, the duration of CuSP increased in patients stimulated at both T3-P3 or Cz EEG locations with more marked changes in CG. The CuSP duration decreased after 1 month (T3) (**Figure 3-17**).

CuSP changes in a representative patient (S16-TG) from the T3-P3 stimulation group are shown in (**Figure 3-16**). CSP and CuSP neurophysiological tests were done before (T1) and three different times after the RTMS (T2, T3, and T4).

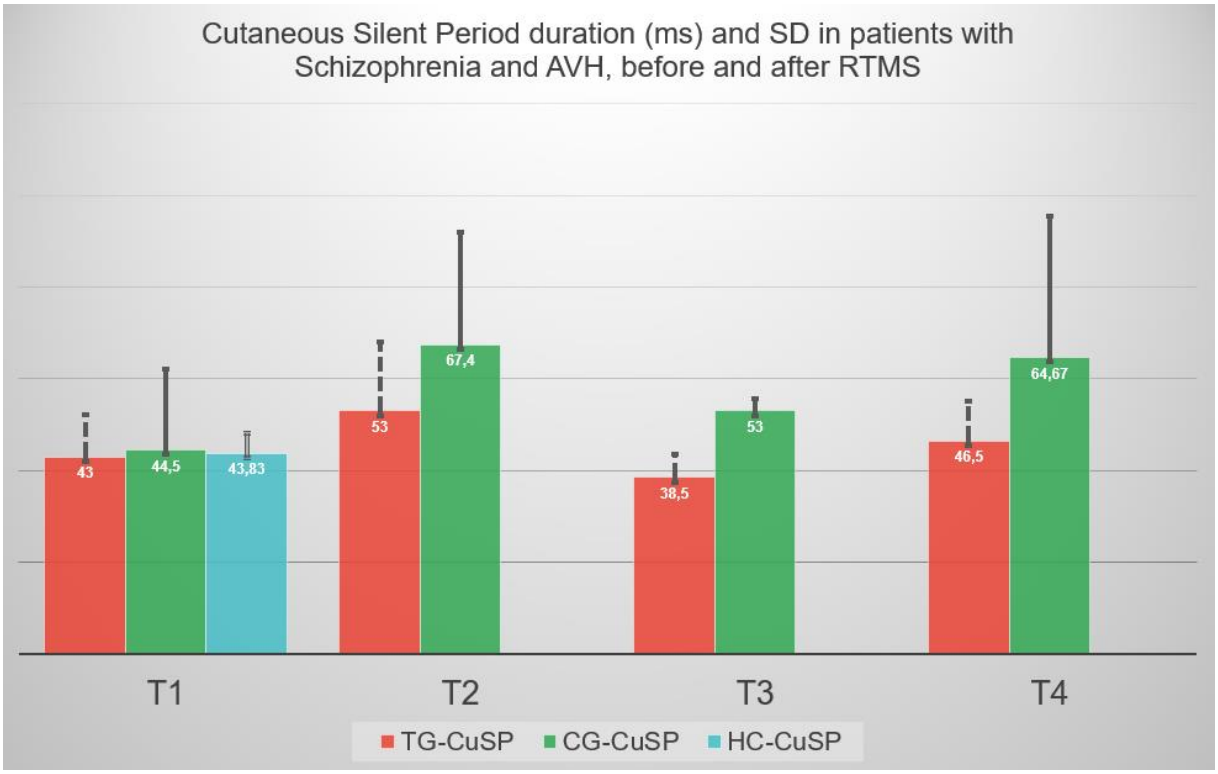


Figure 3-17 *Cutaneous silent period before and after RTMS*

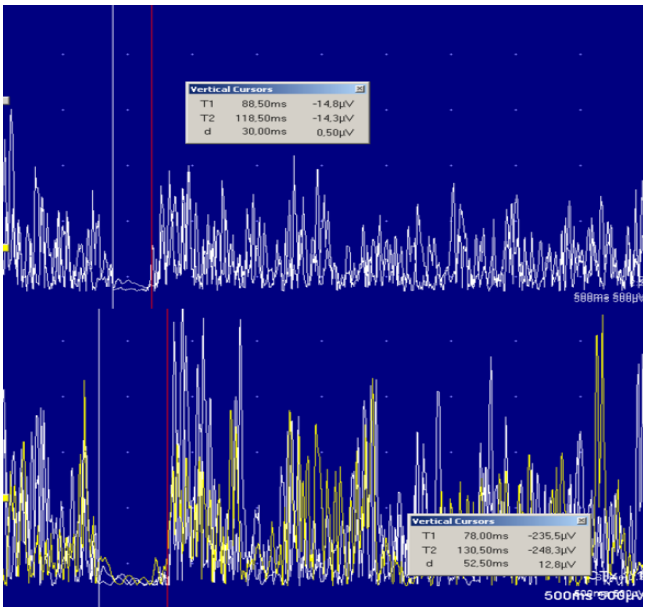


Figure 3-16 *Cutaneous silent period in APB muscle obtained with electricity applied with ring electrodes at 3rd finger (7th dermatome) in a patient with schizophrenia and AVH, S16-TG. The CuSP changed from 30 ms (T1) to 52 ms (T2). Divisions: Y-axis 500 µV and X-axis 500 ms.*

Table 2 *Patients recruited for Cz and T3-P3 RTMS, Study 3.*

Number of participants in CSP and CuSP neurophysiological tests				
Group / Time	*T1 (before RTMS)*	*T2 (after RTMS)*	*T3 (one month)*	*T4 (three months)*
TG	*N4*	*N5*	*N3*	*N3*
CG	*N6*	*N6*	*N4*	*N4*
HC	*N6*			

4 Chapter. Generating hypotheses

4.1 **Study 4.** Effects of transcranial magnetic stimulation on verbal auditory hallucinations and mid latency auditory evoked potentials in patients with schizophrenia and AVH

Banea OC, Jónasson VD, Aubonnet R, Stefansson SB, Magnúsdóttir BB, Haraldsson M, Ívarsson E, Jónasson AD, Sirica R and P Gargiulo (2020). *Not published elsewhere*

In this work, we looked to mid-latency auditory sensory-evoked responses which proved to be of interest in the analysis of sensory gating in patients with schizophrenia.

4.1.1 Methods

Clinical symptoms were used as primary outcomes. Additionally, we measured N1 component (N100) and P2 component (P200) neurophysiological markers as a secondary outcome. A paired-click paradigm was performed to elicit the P50, N100, and P200 components. In this study, we focused on N100 and P200 responses. A pure tone (1500 Hz, 6-ms duration at comfortable hearing level) was created and used to generate a click sound. It was presented through headphones in pairs of identical clicks (S1, initial stimulus, and S2, repeated stimulus) with 500 ms inter-click duration at an interval of 10 seconds between paired stimuli. We presented 150 paired stimuli in five blocks of 30 paired clicks which provided 25 minutes of EEG measurement (Light et al., 2010). Participants were instructed to watch a silent film during the task, to minimize drowsiness and discomfort during the task.

EEG preprocessing and analysis

EEG was recorded using a 256-channel system (ANT Neuro, Netherlands) with an

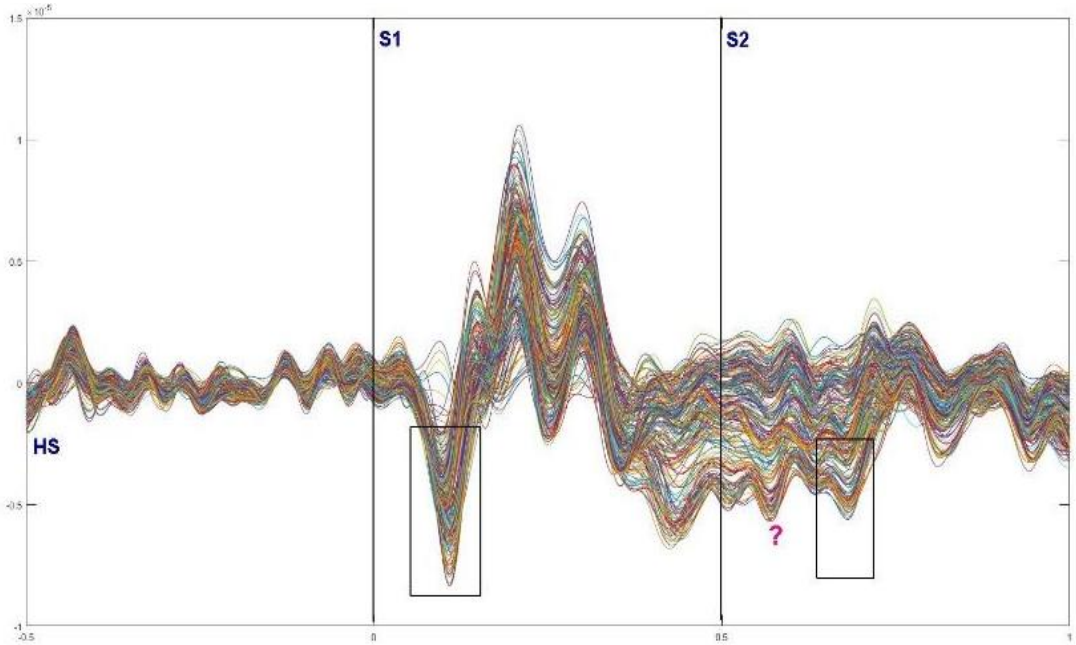


Figure 4-1 *N100-P200 gating in a healthy participant. A delay is observed for S2 corresponding N100-P200 complex.*

electrooculogram (EOG) electrode placed below the right eye and a ground electrode placed on the left side of the neck. Data pre-processing and analysis were performed with Brainstorm (Tadel et al., 2011) and MATLAB 2018b (MathWorks, Inc., Natick, 158 Massachusetts, USA). The data was sampled at 1024 Hz and re-referenced to the average of left and right mastoid electrodes (R19R, L19L). Data were epoched and baseline correction was set at the time when the raw data was imported to Brainstorm. For S1 we used an epoch of 1000 ms (-500 to 500 ms), baseline correction from -500 to -100 ms while for S2 we used an epoch of 1500 ms (-1000 to 500 ms), and baseline correction from -1000 to -600 ms. A bandpass filter was set between 0.5-20 Hz and a notch filter from 49-51 Hz was used to remove undesired monomorphic artifacts from 50 Hz mains electricity. If EEG voltage was higher than ±80 µV the channels were marked as bad. Individual trials were visually inspected and rejected if they contained large muscle artifacts or eye blinks. Rejection rates of more than 30% would indicate poor data quality. Rejection rates between 50 and 70 % would indicate bad data quality and that for the analysis was used a reduced number of trials corresponding to 7.5 to 12.5 minutes out of 25 minutes of EEG recording. For N1 and P2 analyses, the signals were examined separately to avoid S1 to S2 auditory stimuli jitter produced by a possible time gap between the software (code initiating the stimulus generation) and the hardware (stimulus generation) (T. Rosburg, *pers. comm*., Feb 2nd, 2020) (**Figure 4-1**, **Figure 4-2**).

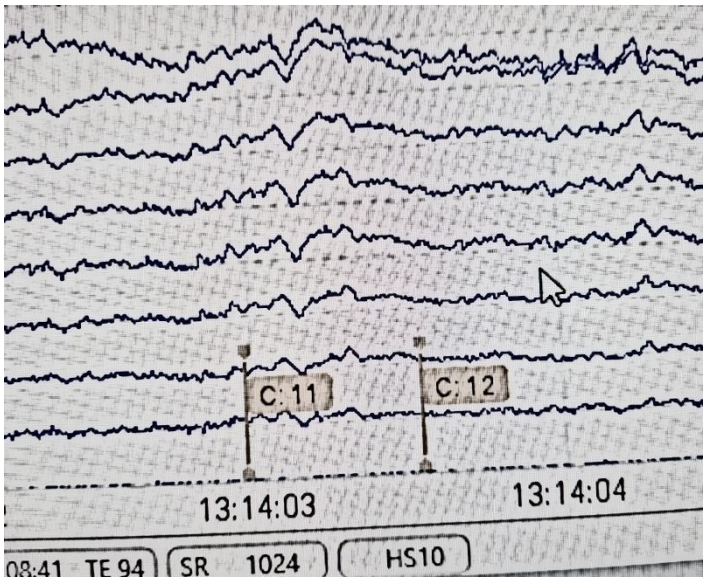


Figure 4-2 *Paired-click paradigm in HS 10 showing the delay of second generated S2 click.*

Variables

The largest negative deflection between 80 and 150 ms was identified as the N100 or N1, and the largest positive deflection between 150 and 250 ms was identified as the P200 or P2. Five different neurophysiological measures of **triggering attention** (N1) and **initial consciousness awareness** (P2) were performed for S1 auditory evoked responses (Figure 4-3):

1) N1S1Bm = N100 amplitude from baseline to the most negative peak in 80 - 150 ms time window range (Clément Nathou et al., 2018),
2) N1S1Mm = N100 maximum amplitude derived from the difference between N100 peak and the previous maximum positive peak
3) P2S1mM = P200 amplitude from preceding N100 trough to the most positive peak (Nashaat N Boutros et al., 2004; Thoma et al., 2017) in 80 - 250 ms time window range,

4) P2S1BM = P200 amplitude from baseline to the most positive peak in 150 - 250 ms time window range and
5) N1S1Lat = N100 peak latency from S1 onset to the most negative peak in the 80-150 ms window range.

For **sensory gating** analysis we calculated eight values for both S1 and S2 stimuli to provide four other metrics (i.e., the ratio between S2 and S1 responses) with two different methods, from baseline (SB) and peak-to-peak (SA):

6) N100SB = S2:S1 baseline amplitude suppression ratio,
7) N100SA = S2:S1 maximum amplitude suppression ratio,
8) P200SB = S2:S1 baseline amplitude suppression ratio,
9) P200SA = S2:S1 maximum amplitude suppression ratio.

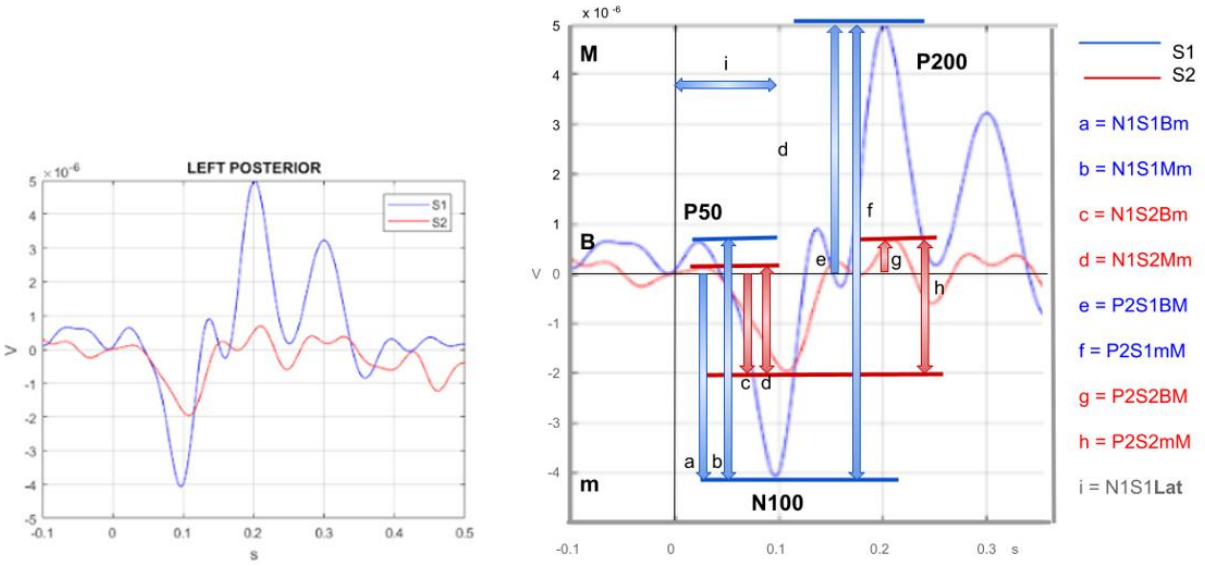


Figure 4-3 *Characteristics of N1 and P2 components. There are different methods of measurement described previously. Conditioning stimulus S1 metrics (blue) and testing stimulus metrics S2 (red).*

For a better understanding of possible local effects on auditory evoked potentials by the left temporoparietal (T3-P3) or vertex (Cz) RTMS, we divided the cortical EEG 256 channels in seven regions of interest (ROI), each of them with an averaged signal derived from 15 electrodes selected from 3 parallel lines (105 electrodes out of a total of 256) (O.C. Banea et al., 2020). The ROI were selected using MATLAB script including the stimulation site and the most representative N100, P200 cortical representation areas as follow: Left Anterior (LA), Left Posterior (LP), Medial Anterior (MA), Medial Central (MC), Medial Posterior (MP), Right Anterior (RA) and Right Posterior (RP). At the end, we measured 9 metrics for each ROI and for the average of all electrodes (AA and AVG) providing 72 (63 + 9) independent metrics.

Statistical analysis was performed with SPSS (version 26). The patient groups were compared to the healthy control group at baseline and the two patient groups were also compared against each other at baseline. Gender comparison was done with a Chi-square test. Outcome measure scores were compared between the two patient groups using ANCOVA when Levene test was non-significant and mixed ANOVA when Levene was significant. If the assumption of sphericity was violated, the Greenhouse-Geisser correction was used. At the end, Bonferroni correction was used to adjust the significance level (i.e., 1 metric in 7 ROI, 7 comp.).

4.1.2 Results

Baseline condition

Patient treatment (TG) and control (CG) groups did not show an age difference. At baseline, there were no significant differences between the two groups on PSYRATS, DASS or QoL. We compared baseline neurophysiological measures between the healthy participants (N=6) and all patients (N=10). From 72 variables, five S1 measures showed significant differences (Table 3, Table 4). N100 and P200 auditory gating metrics (S2:S1) did not show significant differences between the HS and the patients (PG) in baseline condition.

Table 3 *Descriptive statistics for the healthy subjects and patients before the treatment with the variables which showed the most marked changes.*

Variable	Group	Mean	SD
N1S1Bm_LP	PG	-0,57	0,97
	HS	-2,15	1,62
N1S1Mm_MA	PG	1,81	1,61
	HS	4,60	2,00
N1S1Mm_MC	PG	1,67	1,04
	HS	3,80	1,89
N1S1Mm_MP	PG	1,14	0,94
	HS	2,91	1,50
P2S1BM_MA	PG	2,25	1,72
	HS	5,92	3,07

Table 4 *ANOVA, p-value, effect size (η2), and power for the variables showing the most marked changes between healthy subjects and patients in the baseline condition (T1). PG=TG+CG*

Variable	F	p	η^2	Power
HS-PG				
N1S1Bm_LP	6,055	0,027	0,302	0,629
N1S1Mm_MA	9,395	0,008	0,402	0,813
N1S1Mm_MC	8,695	0,011	0,383	0,783
N1S1Mm_MP	8,607	0,011	0,381	0,779
P2S1BM_MA	9,566	0,008	0,406	0,82
AVG			0,374	

Pre-Post RTMS comparison

Clinical outcomes

There were no significant changes in AVH severity measured with PSYRATS AHS global scores after RTMS between TG and CG (H1). After RTMS, PSYRATS AHS global scores decreased from 28 (SD 5.70) to 24 (SD 4.95) for T3-P3 treatment group while for Cz

treatment group it decreased from 30.4 (SD 1.52) to 29 (SD 4.35) ($F = 2.843$, $p = 0.130$, $\eta 2 = 0.262$). From all 11 items, the AVH duration showed a significant difference between pre and post RTMS conditions. It decreased from 2.4 to 2.2 for TG while for the CG it increased from 3.4 to 4.0 ($F = 5.65$, $p < 0.049$, $\eta 2 = 0.447$). QoL global score increased after RTMS with 9.6 out of 112 points in the TG and with 3.6 points in CG (p=0.379) (Table 5) and DASS global score decreased from 52.6 (maximum 126) to 41.8 in TG and from 53.6 to 44.6 in CG as expected, (H2). The null H1 and H2 hypotheses are not true due to type 1 error (no significant changes) and the alternative hypotheses, that both T3-P3 and Cz RTMS treatments produce similar changes to clinical symptoms are not true because of type 2 error (sample size). Even so, all psychometric scales showed similar direction changes of clinical symptoms for both T3-P3 and Cz patient groups.

Table 5 *Changes of psychometric scores at baseline (T1) and after RTMS (T2). AVH duration (in Italic) showed significant change in TG.*

VARIABLE	Group	T1 M(SD)	T2 M (SD)	F	*p*	η^2
PSYRATS						
All				2,843	0.130	0.262
	TG	28.0(5.7)	24.0(4.95)			
	CG	30.4(1.52)	29.0(4.35)			
Frequency						
	TG	3,5	2,8	2,34	0,17	0,251
ANOVA	CG	3,5	3,4			
Duration of AVH						
ANCOVA	TG	2,4	2,2	5,65	*0,049*	0,447
	CG	3,4	4			
Location						
ANOVA	TG	3,8	3	2.13	0,211	?
	CG	2,2	2,2			
Loudness						
ANOVA	TG	1,8	2	0	1	0
	CG	2,2	1,6			
Belief						
ANOVA	TG	2,8	2	4,756	0,066	0,405
	CG	2,2	2,8			
Amount of negative content						
ANOVA	TG	2,2	2,4	0,144	0,716	0,02
	CG	3,4	2,4			
Degree of negative content						
ANCOVA	TG	3,2	2,2	5,378	0,053	0,434
	CG	3,2	3,4			
Amount of distress						
ANCOVA	TG	2,2	2,2	0,001	0,972	0
	CG	3	2,4			
Degree of distress						
ANCOVA	TG	1,6	2,6	1,099	0,329	0,136
	CG	2,4	2,2			
Disruption of life caused by voices						
ANCOVA	TG	1,8	1,4	0,565	0,477	0,075
	CG	2,2	2,2			
Controllability						
ANCOVA	TG	2,6	1,2	3,716	0,095	0,347
	CG	2,6	2,4			
QoL						
Quality of life						
ANCOVA	TG	72	81,6	0,881	0,379	0,112
	CG	74,8	78,4			

DASS						
Depression						
ANCOVA	TG	18,6	14,6	0,069	0,8	0,01
	CG	20,8	17,2			
Anxiety						
ANOVA	TG	14,4	10,8	0,15	0,904	0,002
	CG	13,6	13,2			
Stress						
ANOVA	TG	19.60(18.94)	16.40(14.88)	0,023	0,884	0,003
	CG	19.20(12.19)	14.20(9.63)			

Neurophysiological outcome

The EEG data in the healthy participants had a rejection rate of 38% for S1 and 40 % for S2 and up to 70% for the patient groups (TG: T1S1 62%, T1S2 66%, T2S1 61%, T2S2 63%, and for CG: T1S1 70%, T1S2 70%, T2S1 68%, T2S2 69%). This means that for patients, from the 25-minute EEG record, the analysis was conducted for an EEG record of 7.5 to 12.5 minutes (45 to 75 of the 150 stimuli coupled per click).

TG and CG compared with HS

At baseline condition, 10 out of 72 variables showed an effect size of more than 30 % between HS and TG patients and 12 out of 72 variables showed an effect size of more than 30 % between HS and CG (Table 6). After RTMS, two variables showed the most marked changes for TG with an effect size > 0.3 and $p < 0.05$, while CG didn´t show changes after RTMS. These were N1S1Mm MA or N100 amplitude measured "peak to peak" for the mid anterior region and N1S1Mm MC or N100 amplitude "peak to peak" for the mid-central region. The changes were similar as at baseline condition (**Table 6**) (H3). Sensory gating measurements for N100 and P200 did not show significant changes after RTMS (H4).

Table 6 *Changes of N1 and P2 components HC-TG and HC-CG in baseline (T1) and after RTMS (T2). The variables which showed p<0.05 after RTMS are marked in italic. Here are presented the metrics with an effect size > 0.3 in T1 condition.*

	Baseline				After RTMS			
Variable	F	p	η^2	Power	F	p	η^2	Power
HS-TG								
N1S1Mm_MA	7,29	0,024	0,447	0,672	6,91	*0,027*	0,434	0,649
N1S1Mm_MC	5,17	0,049	0,365	0,528	5,32	*0,046*	0,372	0,539
N1S1Mm_MP	4,88	0,054	0,352	0,505	0,48	0,507	0,05	0,095
P2S1BM_MA	5,18	0,049	0,365	0,529	4,17	0,072	0,317	0,446
P2S1mM_RA	4,84	0,055	0,349	0,501	0,83	0,385	0,085	0,13
N100SA_MC	4,28	0,069	0,322	0,455	2,81	0,128	0,238	0,323
N100SA_MP	6,32	0,033	0,412	0,611	2,78	0,13	0,236	0,319
N100SA_RP	10,47	0,01	0,538	0,82	0,04	0,85	0,004	0,053
P200SA_RP	9,33	0,014	0,509	0,776	1,45	0,26	0,138	0,19
P200SA_AVG	7,62	0,022	0,458	0,691	1,48	0,255	0,141	0,193
AVG			0,412				0,202	
HS-CG								

N1S1Mm_MA	5,02	0,052	0,358	0,516	1,31	0,282	0,127	0,176
N1S1Mm_MC	4,71	0,058	0,344	0,491	0,08	0,781	0,009	0,058
N1S1Mm_MP	5,26	0,048	0,369	0,534	1,38	0,27	0,133	0,184
P2S1BM_MA	5,76	0,04	0,39	0,572	1,81	0,212	0,167	0,225
P2S1BM_MC	4,13	0,073	0,315	0,443	2,82	0,127	0,239	0,324
P2S1mM_MC	5,10	0,05	0,362	0,522	2,95	0,12	0,247	0,336
N1S1Lat_LA	6,99	0,027	0,437	0,654	4,36	0,066	0,326	0,462
N1S1Lat_MP	10,14	0,011	0,53	0,809	0,00	0,975	0	0,05
N1S2Lat_RA	5,72	0,04	0,389	0,569	0,13	0,725	0,014	0,062
N1S2Lat_RP	4,31	0,068	0,324	0,458	0,19	0,674	0,021	0,068
N100SA_MA	4,64	0,06	0,34	0,486	2,05	0,186	0,185	0,249
N100SA_MC	12,75	0,006	0,586	0,887	1,20	0,303	0,117	0,165
AVG			0,395				0,132	

Patient's pre-post analysis

TG and CG neurophysiological data measured separately in pre-post RTMS conditions didn´t show significant changes. Clinical symptoms showed a similar change direction for all psychometric scales: PSYRATS AHS decreased in both groups, QoL improved in both groups and DASS decreased in both groups. The null hypotheses H1 and H2 were not true (type 1 error), and the alternative hypotheses could not be tested because of type 2 error (e.g., for PSYRATS the pre-study calculated N to achieve statistical power was 16). Based on the similar direction of clinical symptoms trends for both groups we suspected that the Cz location RTMS used as control might have induced effects on neurophysiological markers. We calculated pre-post RTMS changes for all 72 metrics in all patients (N=10). Two variables showed the most marked changes after the treatment (**Table 7**, **Table 8**) with small-medium effect size: N1S1BmLP or N100 to S1 measured "baseline to peak" in left posterior region, which changed from -0.57 μV (SD 0.97) to -2.39 μV (SD 1.59), ($p = 0.006$, $\eta2 = 0.346$) and N1S1BmMP or N100 to S1 measured "baseline to peak" in medial posterior region ($p = 0.038$, $\eta2 = 0.218$). Using Bonferroni correction by conducting 7 comparisons (as for each ROI), an adjusted p-value less than 0.00714 would be necessary to accept that N100 amplitude (e.g., N1S1BmLP, N1S1BmMP) change is statistically significant.

Table 7 *RTMS changes induced to MLAEP in patients with schizophrenia and AVH (PG in T1 and T2) (N=10).*

Variable	F	p	η^2	Power
N1S1Bm_LP	9,53	0,006	0,346	0,831
N1S1Bm_MP	5,01	0,038	0,218	0,562

Table 8 *Variables with the most marked changes between baseline (T1) and after RTMS (T2). PG=TG+CG.*

PG T1 – PG T2		Mean	SD	N
N1S1Bm_LP	Pre	-0,57	0,97	10
	Post	-2,39	1,59	10
N1S1Bm_MP	Pre	-0,61	0,88	10
	Post	-1,39	0,66	10

Healthy participants (examples)

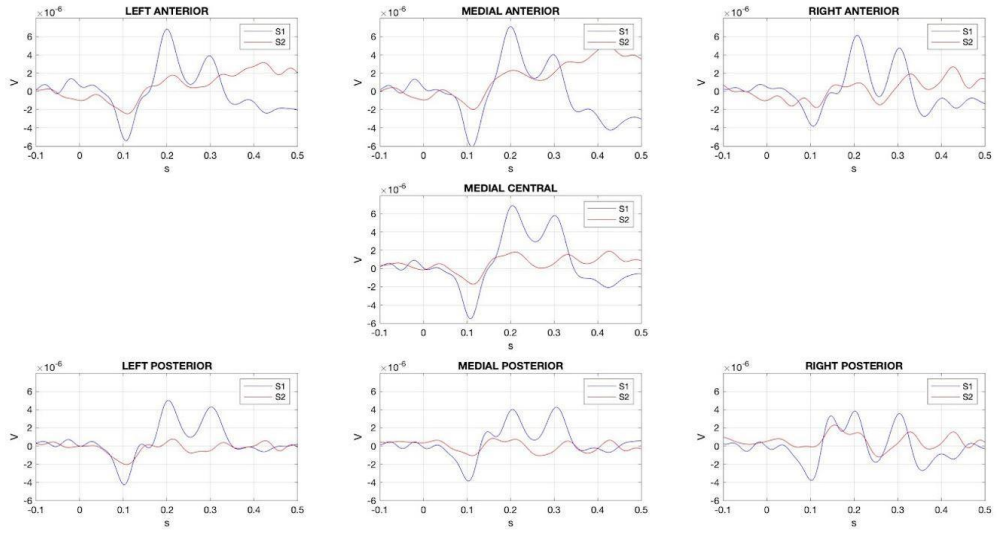


Figure 4-4 *Healthy subject (HS10) N100 and P200 gating cortical topography*

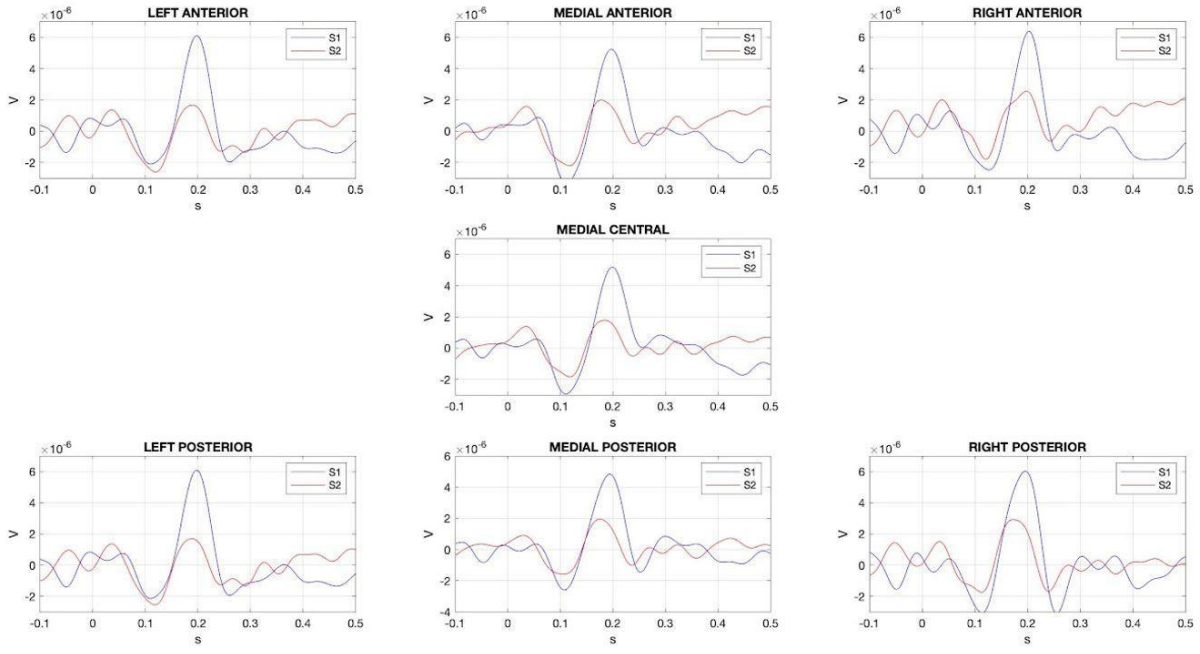


Figure 4-5 *Healthy subject (HS2) N100 and P200 gating cortical topography*

Patients (examples)

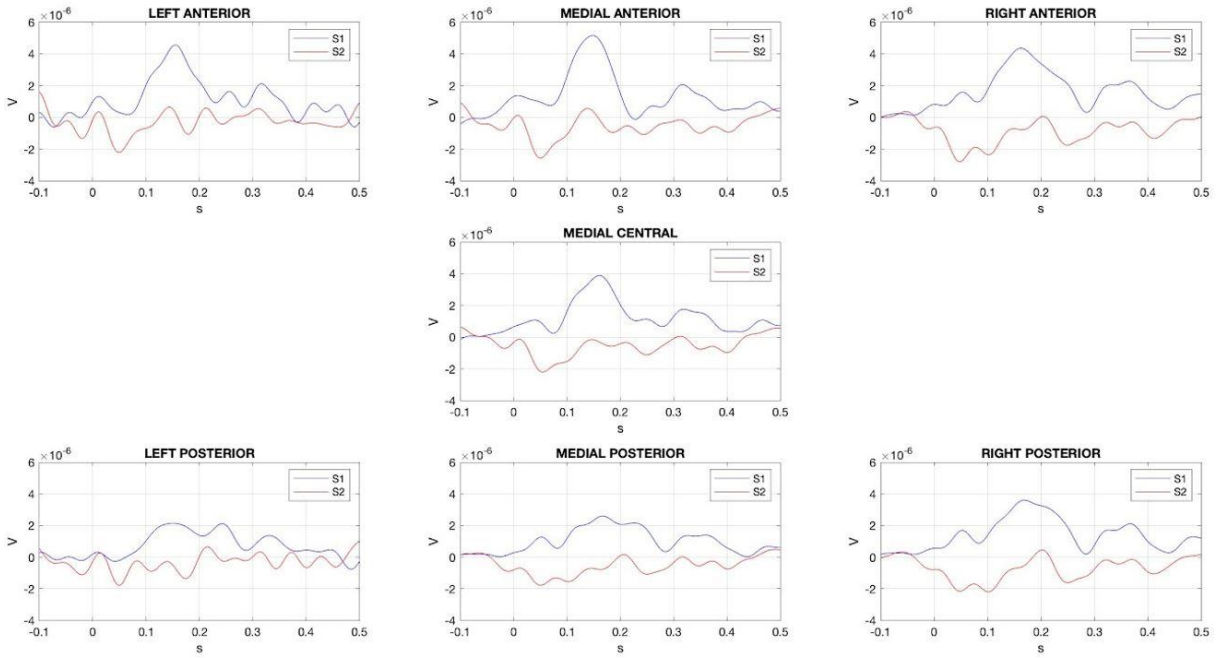


Figure 4-6 *Sensory gating (N1 and P2) in a patient (S25) with SCZ and AVH,* ***Baseline*** *(T1)*

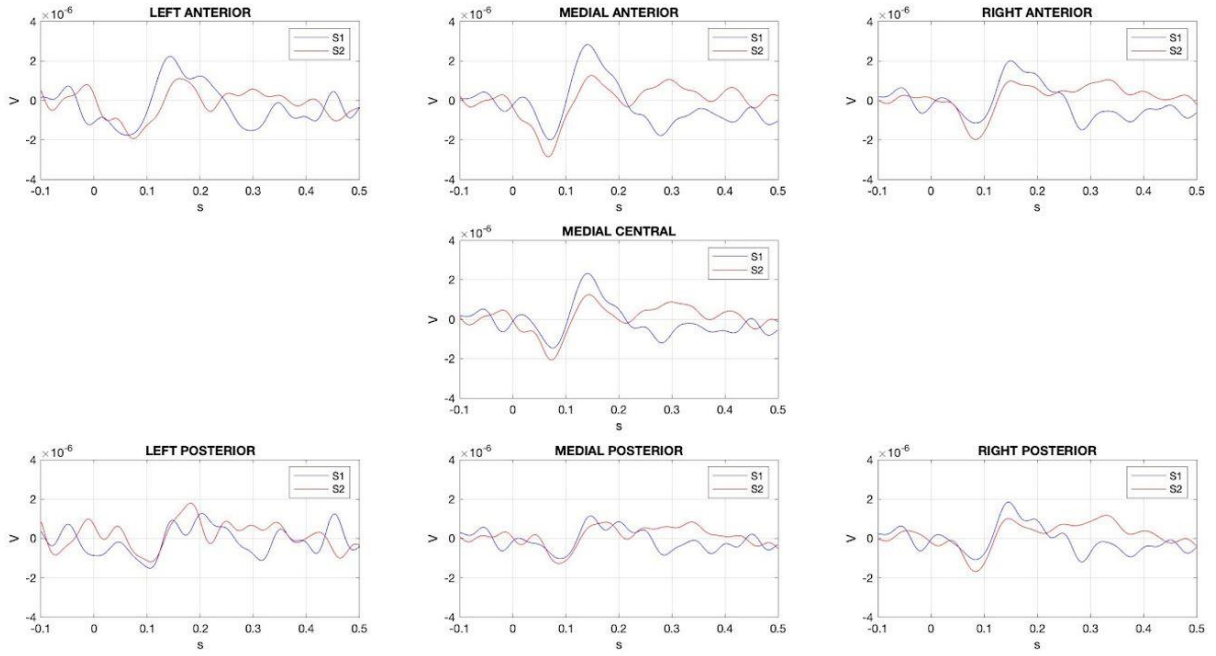


Figure 4-7 *Sensory gating (N1 and P2) in a patient (S25) with SCZ and AVH (T2) after* ***T3-P3 RTMS***

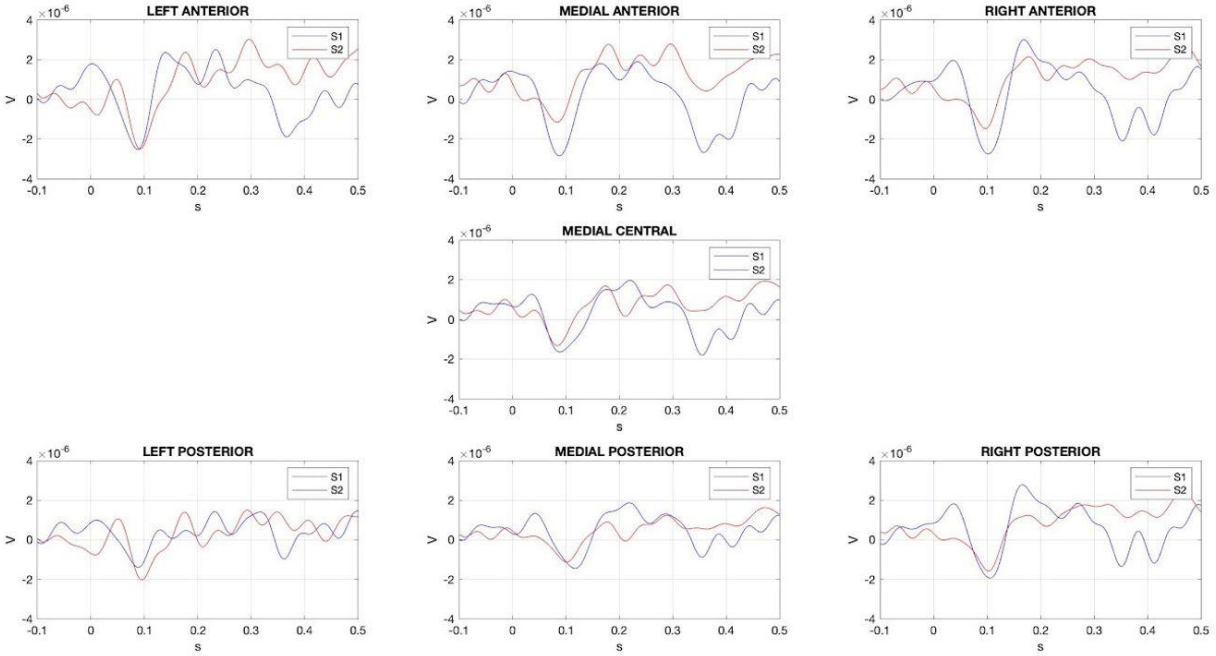


Figure 4-8 *Sensory gating (N1 and P2) in a patient (S16) with SCZ and AVH,* ***Baseline*** *(T1)*

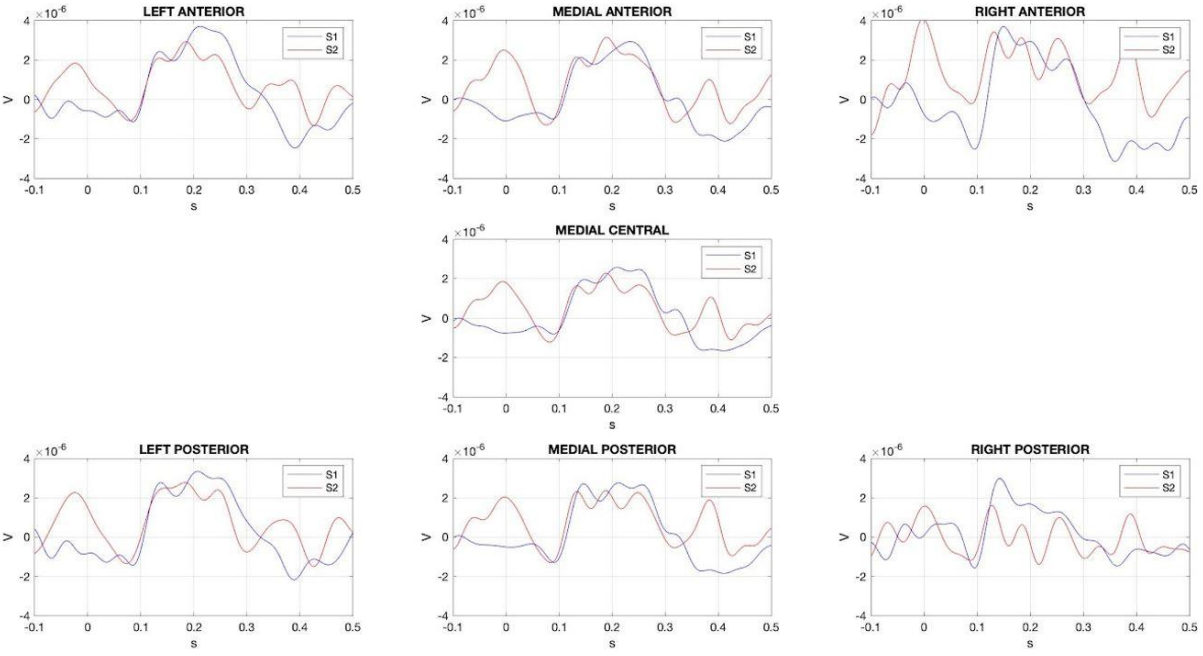


Figure 4-9 *Sensory gating (N1 and P2) in a patient (S16) with SCZ and AVH (T2), after* ***Cz RTMS***

4.2 **Study 5.** P300 Analysis Using High-Density EEG to Decipher Neural Response to RTMS in Patients with Schizophrenia and Auditory Verbal Hallucinations (Aubonnet et al., 2020)

Here, we compared alterations in the P300 response after left temporal and vertex RTMS in patients with schizophrenia using three different approaches: time, frequency, and source-space connectivity. We remained descriptive in our analysis before and after treatment, at group and single levels.

4.2.1 Methods

P300 Recordings

P300 was measured with an auditory oddball paradigm attention task. The recordings took place between 11h00 and 14h00 for a duration of 1 h. The subjects sat with their eyes closed. The frequent (F) and the rare (R) auditory stimuli were presented binaurally through headphones at an interstimulus interval between tones of constant 1.1 s (Möller et al., 2009). The loudness was adjusted for each participant. For each subject, there was one trial of 200 tones, comporting a random tone occurrence with a probability of 0.2, leading to 160 frequent tones and 40 rare. We required the participants to focus on the rare stimuli without counting or moving a finger.

EEG Pre-processing and Analysis

The EEG was recorded using a 256-channel system (ANT Neuro, Netherlands) with an electrooculogram (EOG) electrode placed below the right eye and a ground electrode placed on the left side of the neck. Data pre-processing and analysis were performed with Brainstorm (Tadel et al., 2011) and MATLAB 2018b (MathWorks, Inc., Natick, 158 Massachusetts, USA).

Pre-processing

The data were sampled at 1,024 Hz and re-referenced to the average of left and right mastoid electrodes (R19R, L19L). A bandpass filter was set between 0.5 and 70 Hz and a notch filter from 49 to 51 Hz was used to remove undesired monomorphic artifacts from 50 Hz mains electricity. Bad channels were manually removed when EEG voltage was higher than ±80 μV; if more than 10% of the channels showed too much noise or incorrect signal, the whole trial was rejected. The signals were digitized in epochs of 1,200 ms, starting 500 ms before the presentation of each auditory stimulus (–500 to +700 ms). Baseline correction was performed using pre-stimulus 500 ms to pre-stimulus 100 ms window and channels marked as bad were removed and interpolated. Individual trials were visually inspected and rejected when indicative of excessive muscle activity, eye movements, or other artifacts (**Figure 4-11**).

Data Analysis

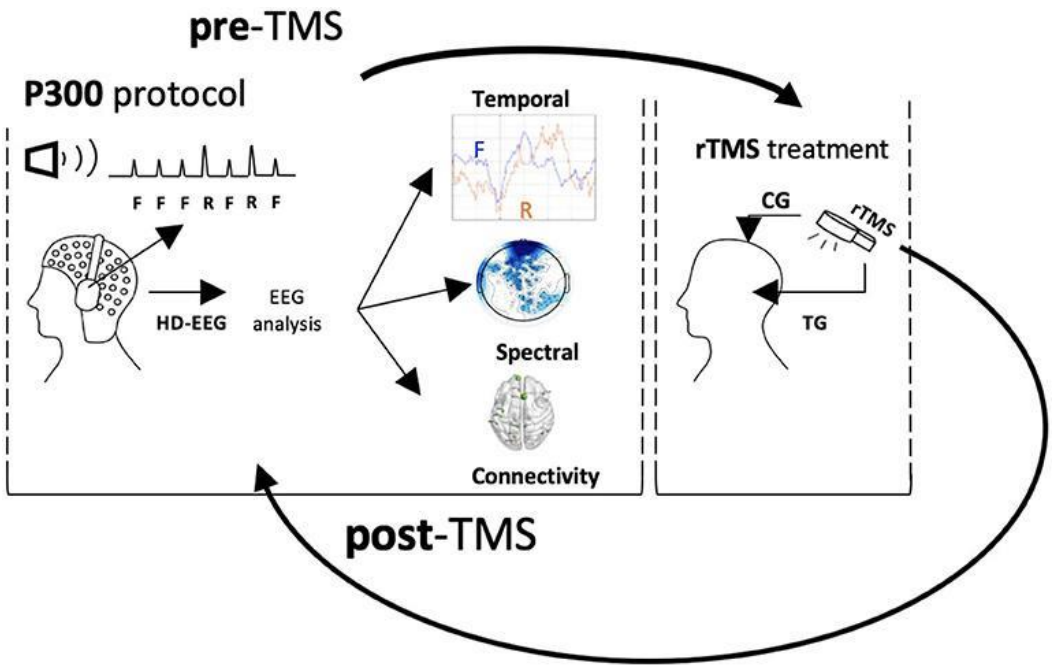


Figure 4-10 *P300 protocol, QEEG and RTMS design. Study 4*

Frequency Domain

The power spectral density (PSD) was computed for each epoch with Welch's method, using Brainstorm, with the following frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), gamma (30–70 Hz). The PSD has been divided by the associated bandwidth for each frequency band.

Using the same scalp division as that of the time analysis, the PSD of electrodes within the same ROI were averaged for frequent and rare stimuli, pre- and post-treatment for each subject. The PSD difference T2-T1 and frequent-rare were computed for each subject.

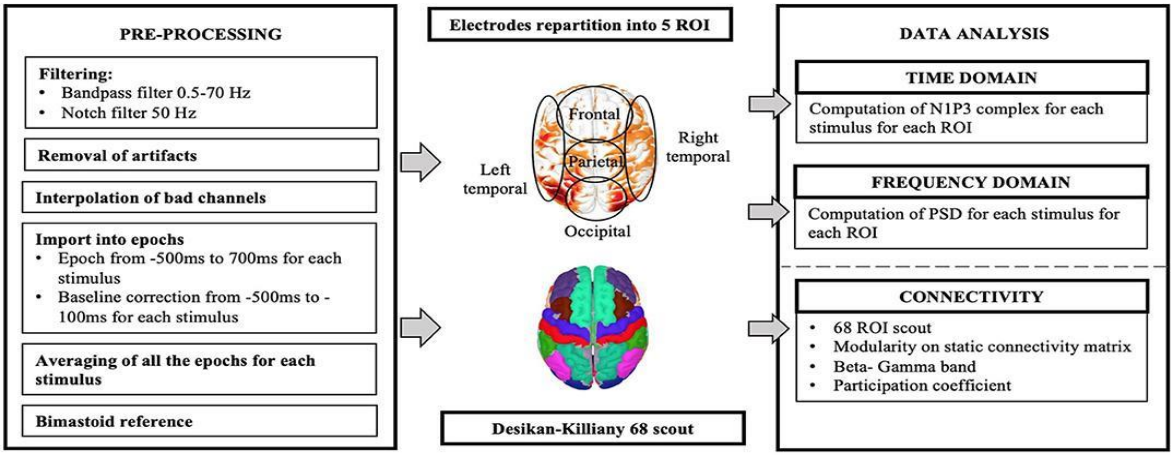


Figure 4-11 *Study 4, methods.*

Time Domain

N100-P300 complex values of both frequent and rare stimuli were calculated and plotted via MATLAB 2018b for each subject (pre- and post- treatment for patients' groups).
The scalp was divided into 5 regions of interest (ROI). The 254 electrodes were partitioned as follows: 80 channels for the Frontal region (F), 59 for the Parietal region (P), 69 for the Occipital region (O), 23 for the Right Temporal lobe (RT), and 23 for the Left Temporal lobe (LT) (Schartner et al., 2015). N1-P3 wave signals were calculated for the entire N100-P300 complex from the average of channels of every ROI as the difference between the most negative voltage value within the time range of 80–150 ms (N100) and the most positive voltage value within the time range of 250–500 ms (P300). The differences between frequent and rare stimulus and T2-T1 treatment were also computed and plotted.

Connectivity

The connectivity has been computed at the cortical level using the "EEG source connectivity" method. It consists of estimating the brain sources (over 68 regions of interest - ROI) and then computing the statistical coupling between these reconstructed sources. The weighted minimum norm estimate (wMNE) and the Phase Locking Value (PLV) was used to solve the inverse problem and compute the functional connectivity, respectively. The analysis has been performed only on the beta and gamma bands, due to window length constraints (here 700 ms). The source-space networks were estimated for each trial, subject and condition. The networks were quantified using network measures that allow the extraction of the topological properties of the networks. To quantify the network integration, we used the participation coefficient (PC), to calculate the interactions between brain modules (distant sub-networks), on the threshold connectivity matrices (here 20%). We used the brain connectivity toolbox[12] (BCT) to compute the PC (Rubinov & Sporns, 2010).

4.2.2 Results

The individual analysis revealed general consistent results. The analysis of the psychometric tests revealed that four out of five subjects in TG and three out of five subjects in CG felt improved condition after the treatment, whereas the other subjects remained neutral or reported worse psychometric scores. In the time domain analysis, the N1-P3 amplitude was globally higher post-treatment than pre-treatment, for six subjects, two in TG and four in CG. The PSD increased post-treatment mainly for the alpha band and beta band globally, for six subjects as well, two in TG and four in CG. No trends were detectable for the gamma and theta bands. In several subjects, the right temporal area showed an opposite behavior compared to the other regions. The connectivity results showed an increased network integration (increase in participation coefficient) during post-treatment for frequent, for the beta band especially, for seven subjects, four in CG, three in TG. There were no significant changes in AVH severity measured with PSYRATS AHS, in QoL and DASS global scores after RTMS between TG and CG (Aubonnet et al., 2020).

Study cases

Due to the small sample size and high variability of the results, cases are discussed individually. The following four patients were selected due to their interplay between

[12] http://www.brain-connectivity-toolbox.net

psychometric score and neurophysiological results, independent of treatment. Two subjects (S17, in TG and S23, in CG) presented an improvement in the psychometric score post-TMS, and the two others presented a stagnation in the psychometric (S26, in CG) or a decrement (S15, in TG).

Improvement in Psychometric Score

The two patients detailed in this section presented an improvement in their psychometric score post-treatment. We chose to describe them in this section due to their higher values post-treatment in the neurophysiological data.

Patient S17-TG

Patient S17 is a man with paranoid schizophrenia, in the TG, who took part in the study while taking Clozapine, Olanzapine, Perphenazine, Alprazolam, Levomepromazine, Oxazepam, and Melatonin. The psychometric tests showed an improvement of the QoL, a decreased DASS, and decreased PSYRATS in T2 (after RTMS). The temporal analysis showed a lower N1-P3 amplitude post-treatment, except for the parietal and left temporal parts. The PSD showed higher alpha power post-TMS. However, the beta power is lower post-TMS. The connectivity revealed a clear higher participation coefficient (represented by the larger green nodes), especially in the left central, left orbitofrontal, and the right occipital brain regions. The frontal area showed a relatively lower participation coefficient. (**Figure 4-12**)

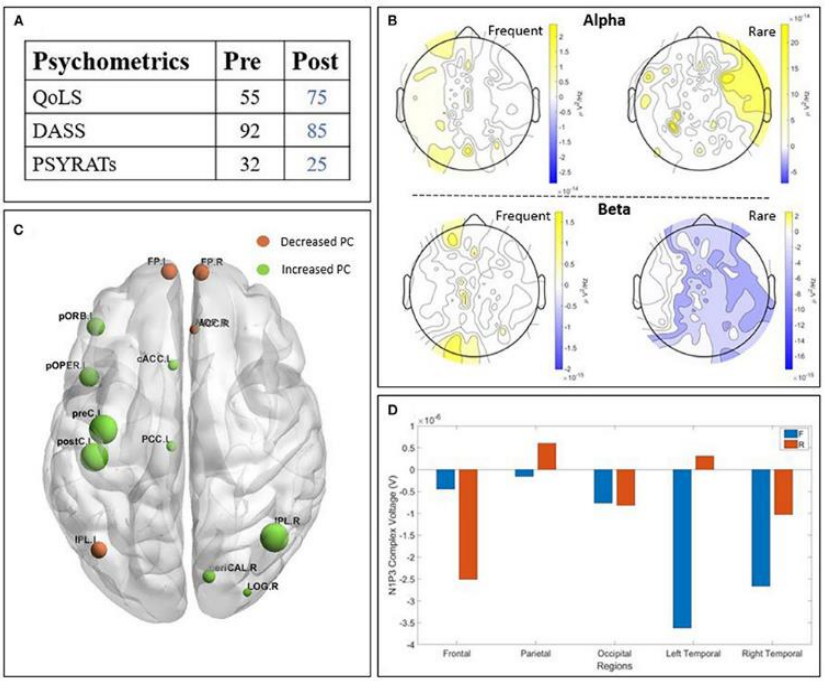


Figure 4-12 *Results of patient S17-TG: (A) psychometric; (B) Scalp-level frequency analysis; (C) Source-space connectivity; (D) Scalp-level time analysis. The yellow areas in frequency analysis are related to a higher PSD in T2, whereas the blue ones are related to a higher PSD in T1. The size of the node in the connectivity is related to the amount of increase (green) or decrease (orange) participation coefficient (PC) values. The positive bars in time analysis are related to a higher N1-P3 amplitude in T2, and the negative bars show lower amplitude of the N1-P3 complex in T2.*

Patient S23-CG

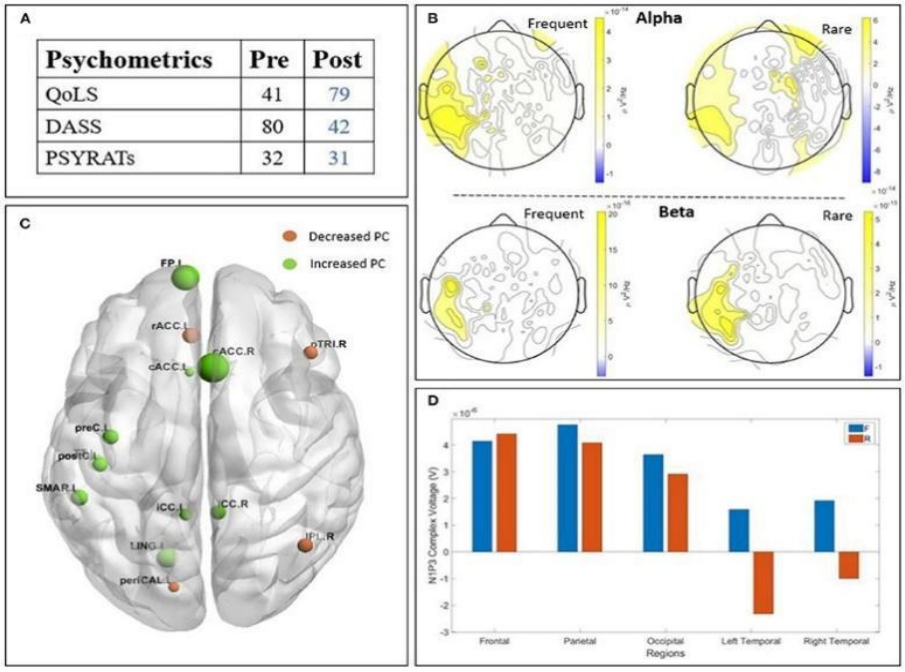


Figure 4-13 *Results of patient S23-CG: (A) psychometric; (B) Scalp-level frequency analysis; (C) Source-space connectivity; (D) Scalp-level time analysis. The yellow areas in frequency analysis are related to a higher PSD in T2, whereas the blue ones are related to a higher PSD in T1. The size of the node in the connectivity is related to the amount of increase (green) or decrease (orange) participation coefficient (PC) values. The positive bars in time analysis are related to a higher N1-P3 amplitude in T2, and the negative bars show lower amplitude of the N1-P3 complex in T2.*

Patient S23 is a woman with paranoid schizophrenia, in the CG, who took part in the study while taking: Aripiprazole, Olanzapine, Chlorprothixene, and Pregabalin. The psychometric outcome revealed an improvement after the treatment. The QoL increased, the DASS decreased, while the PSYRATS did not change. The time-domain analysis showed a higher amplitude of the N1-P3 complex after the treatment, except on the temporal regions for the rare stimulus. The PSD showed higher alpha power in T2, except the right temporal region for both frequent and rare stimuli. The beta band also showed a higher PSD in T2. Finally, the connectivity study displayed a globally improved participation coefficient, principally in the frontal, occipital, and central areas of the brain (**Figure 4-13**).

Stagnation in Psychometric Score

The patient detailed in this section presented a stagnation in her psychometric score post-treatment

Patient S26-CG

Patient S26 is a woman with paranoid schizophrenia, in the CG. Her treatment included Clozapine, Flupenthixol, Zopiclone, Mirtazapine, Escitalopram, Metformin, Metoprolol, and Chlorpromazine. The psychometric data showed that RTMS treatment did not have a lot of impact on this scale. The QoL, DASS, and PSYRATS remained similar in T2. The time-domain showed a global increase of N1-P3 amplitude post-TMS, except for the parietal region for both stimuli and the frontal region for the frequent stimulus. The PSD analysis showed higher alpha and beta power in T2 (except for frontal frequent stimulus responses in the alpha band).

The connectivity analysis revealed a balanced participation evolution. Globally the left hemisphere (mainly the entorhinal and frontal) showed a decreased participation coefficient,

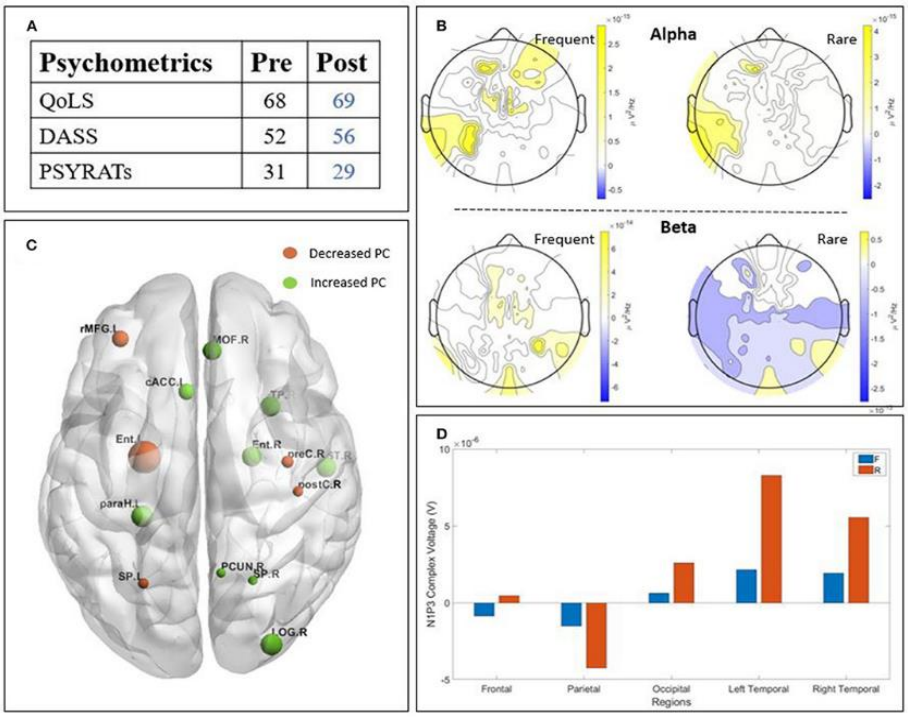


Figure 4-15 *Results of patient S26-CG: (A) psychometric; (B) Scalp-level frequency analysis; (C) Source-space connectivity; (D) Scalp-level time analysis*

and the right areas (mainly the frontal and occipital) showed an increased participation coefficient (**Figure 4-15**).

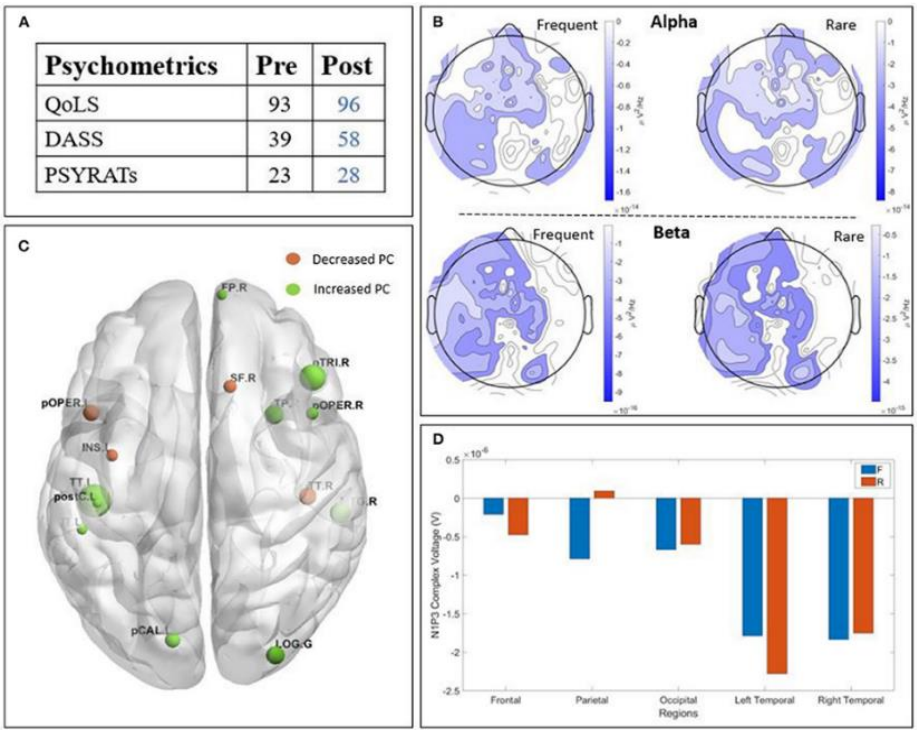


Figure 4-14 *Results of patient S15-TG: (A) psychometric; (B) Scalp-level frequency analysis; (C) Source-space connectivity; (D) Scalp-level time analysis.*

Decrease in Psychometric Score

The patient detailed in this section presented a decrease in psychometric score post-treatment.

Patient S15-TG

Patient S15 is a man with paranoid schizophrenia, in the TG, who took part in the study while taking: Clozapine, Amisulpiride, Propranolol, and Clonazepam. The psychometric data showed very little effect of treatment on this scale. The QoL remained the same, the DASS increased and the PSYRATS slightly increased. The time-domain showed a global decrease of N1-P3 amplitude post-TMS (mostly for the deviant stimulus at the left temporal region) and showed a slight deviant stimulus increment at the parietal region. The PSD analysis showed a lower alpha power in T2, except for the right temporal region. The beta power decreased as well, except for the right temporal region for the frequent stimulus. The connectivity analysis showed a globally higher participation coefficient in the right frontal, left central, and occipital brain regions (Figure 4-14).

4.3 **Study 6.** Network signatures of RTMS treatment in patients with schizophrenia and auditory verbal hallucination during an auditory-motor task using HD-EEG (Ovidiu C. Banea et al., 2021)

The results from the exploratory work (***Study 2***) showed that the auditory-motor task triggers a stable network that is held active throughout the task. Cortical activity seemed to be reduced in the schizophrenia participant during the AM task and after the treatment, the EEG cortical activity was increased and fragmented. The "bird-eye" view maps are not sufficient to quantify the possible change induced by RTMS in patients with schizophrenia.

The objective of this work was to identify a robust methodology of quantifying the EEG data obtained from different regions involved in the auditory-motor brain functional networks. Network organization was analyzed with graph theory, especially with characteristic path length and small worldness effect.

4.3.1 A multimodal approach assessing changes in brain connectivity

Previous work-up of recorded EEG data during the auditory-motor task

Although EEG PSD could characterize the group differences between the HS group and the patients with schizophrenia and AVH in the frequency domain, it only focuses on single-channel EEG and cannot reflect the relation between different EEG series (i.e., the connection between different brain areas). MATLAB codes were applied to collect relative power (RP) data from the absolute power obtained with FFT, PSD was calculated, and RP "bird-eye" view maps were plotted. Initially, data were obtained for the HS group by averaging the signal obtained from 17 electrodes in each area of interest. The index of the T2/T1 ratio was used to assess the change in relative power obtained from all regions.

Index of brain plasticity

Brain plasticity is an intrinsic property that enables it to adapt to variations in the environment, physiologic changes, and new experiences. Plastic changes occur by modifying pre-existing neuronal connections through changes in cortico-cortical and cortico-sub-cortical networks in response to new afferent impulses or efferent demands. Changes have a place at the molecular and cellular levels and can be followed by the establishment of new dendritic growth (Pascual-Leone et al., 2005). In 2017, Amo et al., described an index of plasticity for the motor cortex as the ratio between gamma-band activity (GBA) induced to event related-synchronization (ERS) EEG obtained after a given task (e.g., moving a finger) divided by GBA at baseline condition (Amo et al., 2017). We followed the same method to describe the temporal change of the induced and evoked oscillations to the motor cortex, but also to other regions like auditory cortices or frontal regions. Moreover, we applied this method described by Amo et al. (2017) in patients with schizophrenia and AVH, using data from four regions of interest (also out of motor cortex) obtained before and within one week after RTMS. We constructed histogram graphs to look at data distribution across the areas of interest. This approach serves also to detect outliers.

Background

The offline modulatory effects of repetitive TMS on neural oscillations are less investigated. There is a general agreement that decreases in EEG power reflect oscillatory aspects of cortical activation (i.e., *arousal*) while increases in EEG power have been associated with predominantly inhibitory activities. Here we looked at T3-P3 and Cz RTMS offline effects on EEG spectral relative power within one week after 10 days of RTMS treatment for patients with schizophrenia and AVH during the auditory-motor task (see ***Study 2***). We analyzed data locally from four regions of interest (ROIs): contralateral and ipsilateral hand sensorimotor regions (CSM and ISM) and contralateral temporoparietal (CTP) and ipsilateral temporoparietal (ITP) regions. We hypothesized that beta activity would show higher (*mu* desynchronization) relative power over contralateral (CSM) and ipsilateral sensorimotor (ISM) hand regions after RTMS (H1) and that gamma relative power would increase after RTMS in all 4 ROIs.

Methods

Five patients (mean age = 32,4, three males, two females) and two healthy subjects (mean age = 24,5, one male) were included in this study.

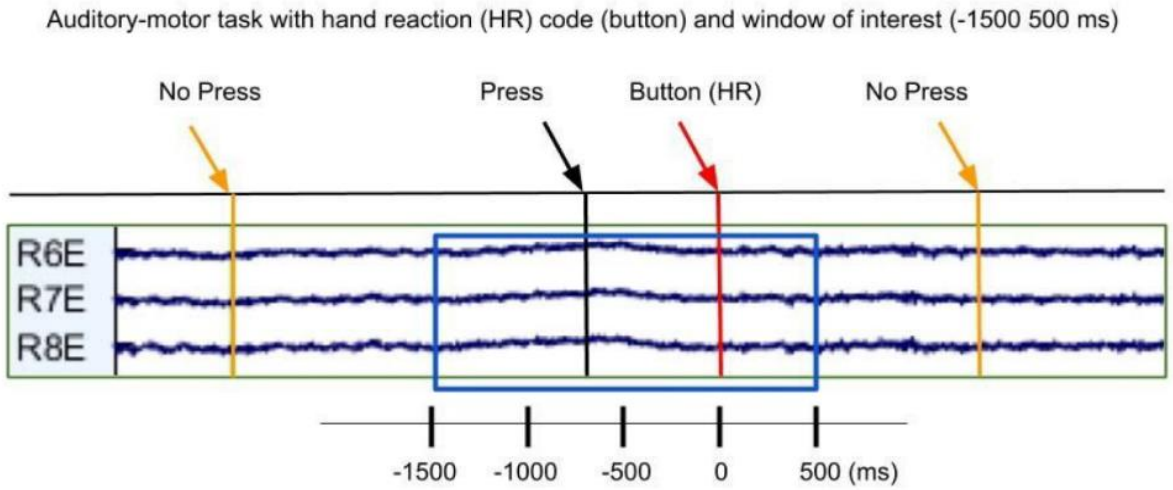


Figure 4-16 *The window of interest during AM Task including Bereitschaftspotential. Work-up to assess index of brain plasticity (offline RTMS aftereffects) in patients with schizophrenia and AVH.*

Raw EEG was exported and further analyzed by a series of customized codes using Brainstorm and ASA software. The raw EEG signals were filtered between 2 and 70 Hz, with a 50 Hz notch filter, before the trials were epoched −1500 to 500 ms relative to the button "press" code (hand reaction) (Figure 4-16). The time window was determined to include the readiness potential window or *Bereitschaftspotential* (Jahanshahi & Hallett, 2003). Before averaging the epochs, baseline correction was performed using the 100ms prestimulus interval. Epochs were later averaged and FFT was applied to 30-40 trials of 2 seconds (evoked oscillations). To measure the relative power of each band, the raw EEG was separated into delta (2–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), low beta (13–18 Hz), high beta (18–30 Hz), and gamma (30–70 Hz). The signal was processed from 4 regions of interest (ROI) including both sensorimotor cortices (SM) and both supratemporal gyri and temporoparietal regions (TP). Each ROI contained 17 electrodes. FFT and ROI analyses were performed using MATLAB scripts. To assess changes between pre and post RTMS we used the T2 (post RTMS) / T1 (pre RTMS) ratio as an index of plasticity (e.g., GBA index would be the relative power of the gamma band during AM task performed after RTMS divided to gamma power during AM task performed in baseline condition). An index > 1 suggests increased relative power after RTMS and < 1 suggests decreased relative power after RTMS).

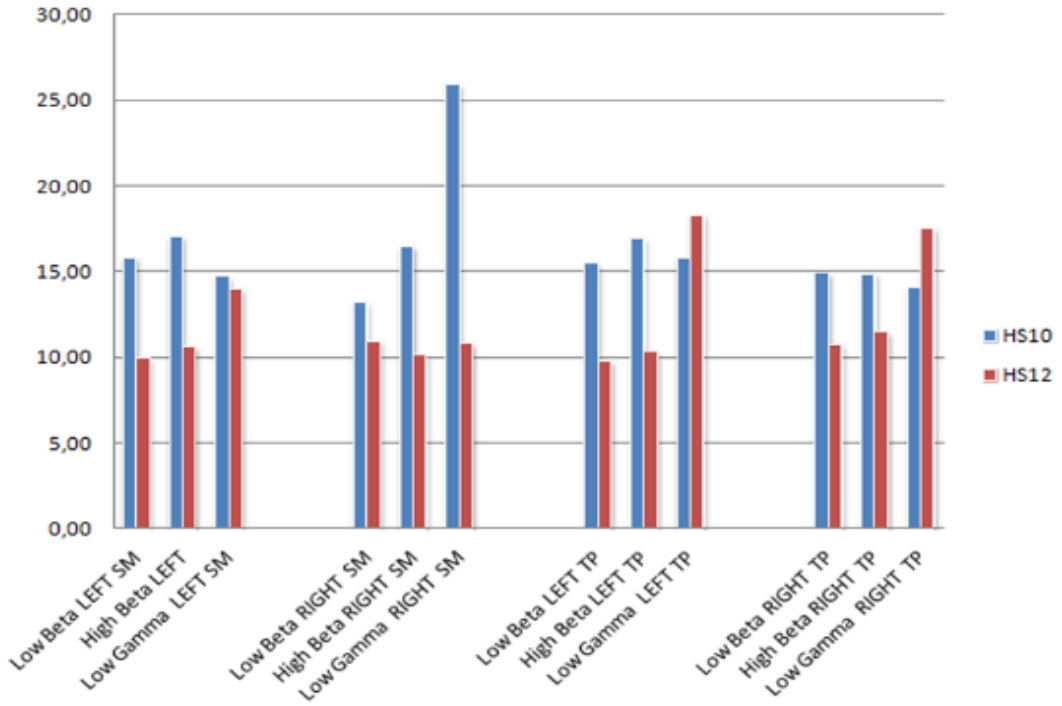
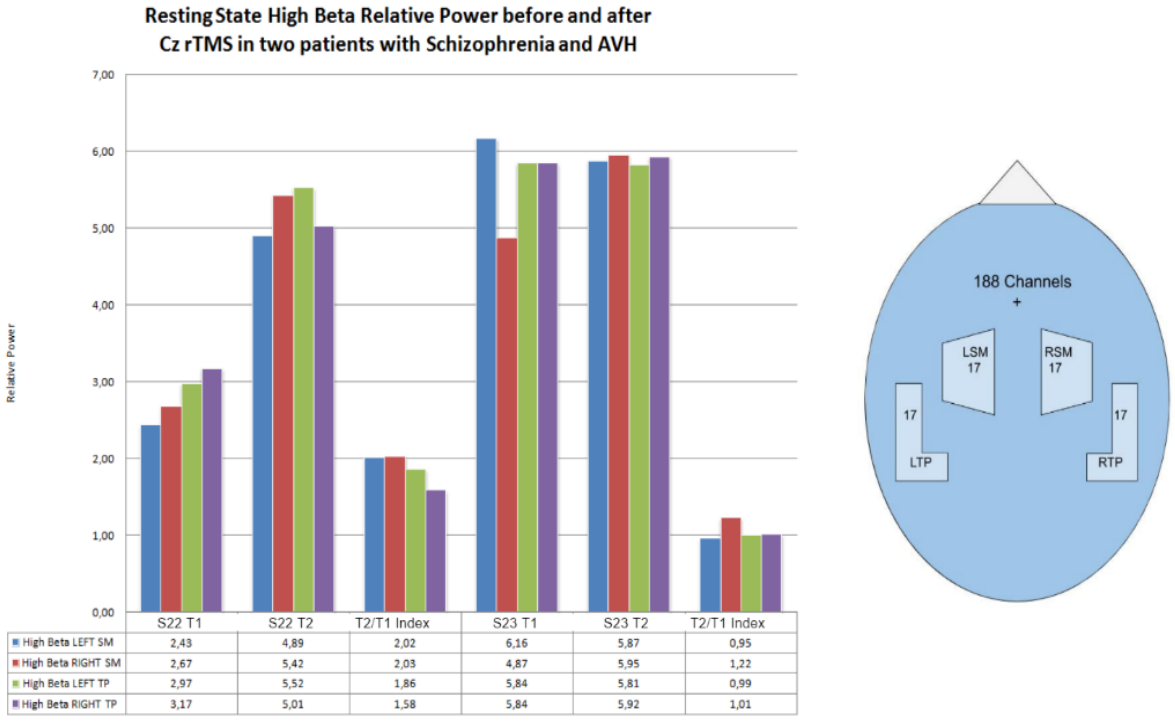


Figure 4-17 *Relative power (%) Low beta, High beta, and gamma EEG distribution over sensorimotor (SM) and temporoparietal (TP) regions. Data are presented for two healthy subjects during the resting state.*

Results - Resting State

In ***resting-state*** conditions, HS showed higher low beta and high beta activity in comparison with the patients (**Figure 4-17**, **Figure 4-18**). After RTMS, the S22 patient showed increased relative power of high beta in all four regions (**Figure 4-18**).



	S22 T1	S22 T2	T2/T1 Index	S23 T1	S23 T2	T2/T1 Index
High Beta LEFT SM	2,43	4,89	2,02	6,16	5,87	0,95
High Beta RIGHT SM	2,67	5,42	2,03	4,87	5,95	1,22
High Beta LEFT TP	2,97	5,52	1,86	5,84	5,81	0,99
High Beta RIGHT TP	3,17	5,01	1,58	5,84	5,92	1,01

Figure 4-18 *Resting state EEG High Beta band changes after Cz RTMS in two patients, S22 (first three columns - T1, T2 and T2/T1 and S23 (columns at right t1, T2, T2/T1).*

After RTMS (T2/T1 index)

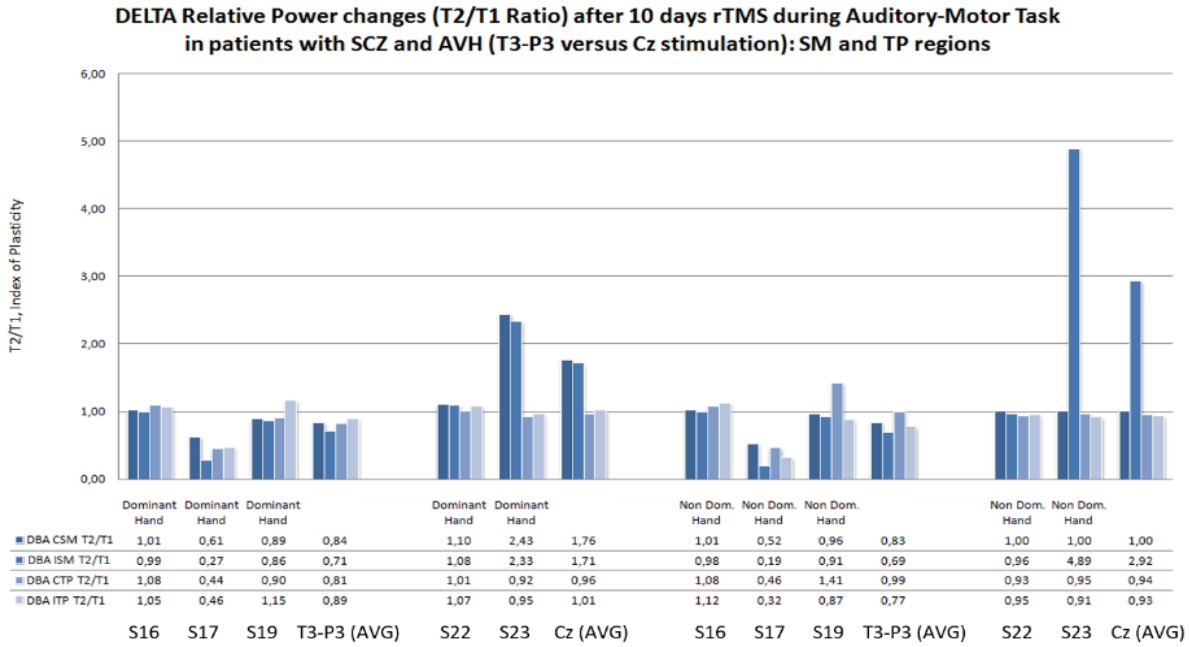


Figure 4-19 *Delta activity changes during AM task. It is visible how the S23 patient showed visible change over (ipsilateral SM) central region (state of drowsiness?).*

Low Beta index showed maximum changes (in the patient S17, TG) over ipsilateral SM and both TP regions while the task was performed with the non-dominant hand, contralateral SM cortex showed a decreased low beta band index (**Figure 4-21**). No visible changes were seen when the task was performed with the dominant hand.

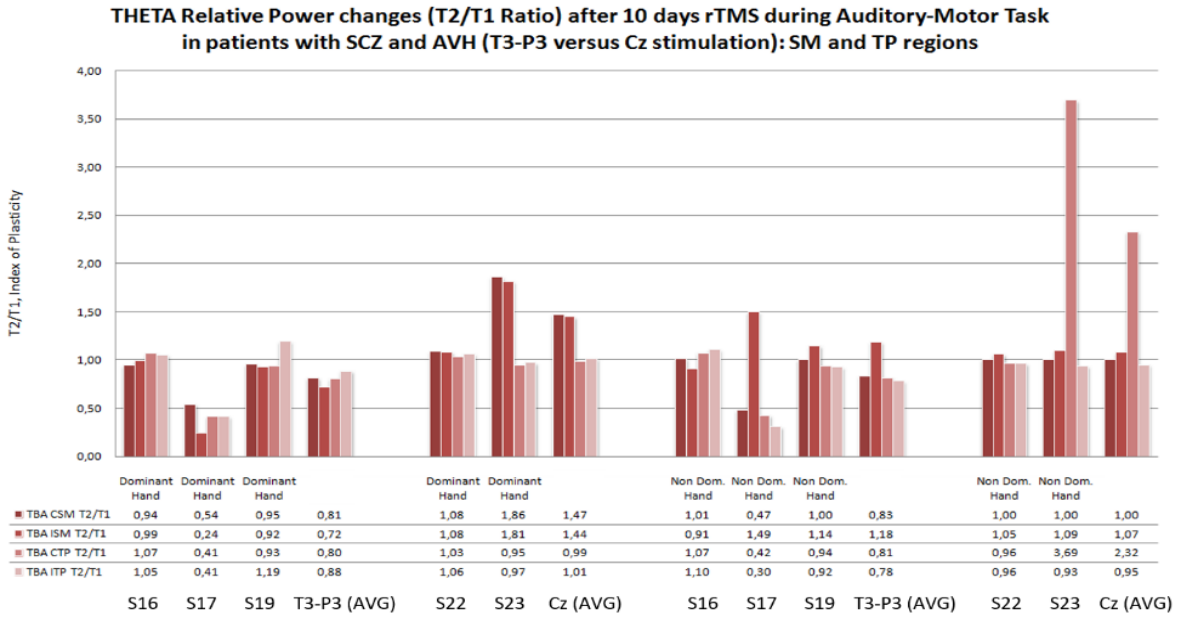


Figure 4-20 *Theta band activity changes during AM task after RTMS*

High Beta index was generally below 1 with a patient (S17-TG) showing indexes < 0.5 in all ROI while the task was performed with the dominant hand. The highest positive change

was seen over the left temporoparietal region while the task was performed with the left (non-dominant) hand (HBBA ITP = 2.88) (**Figure 4-23**).

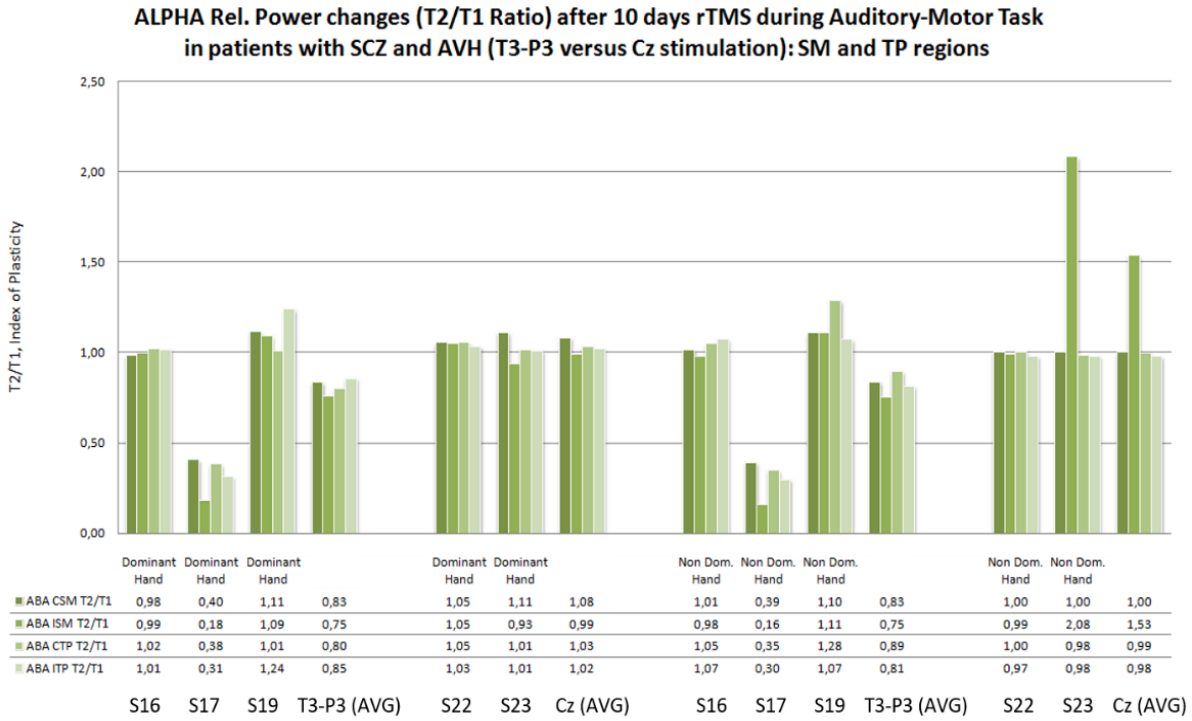


Figure 4-22 *Alpha band activity changes during AM task.*

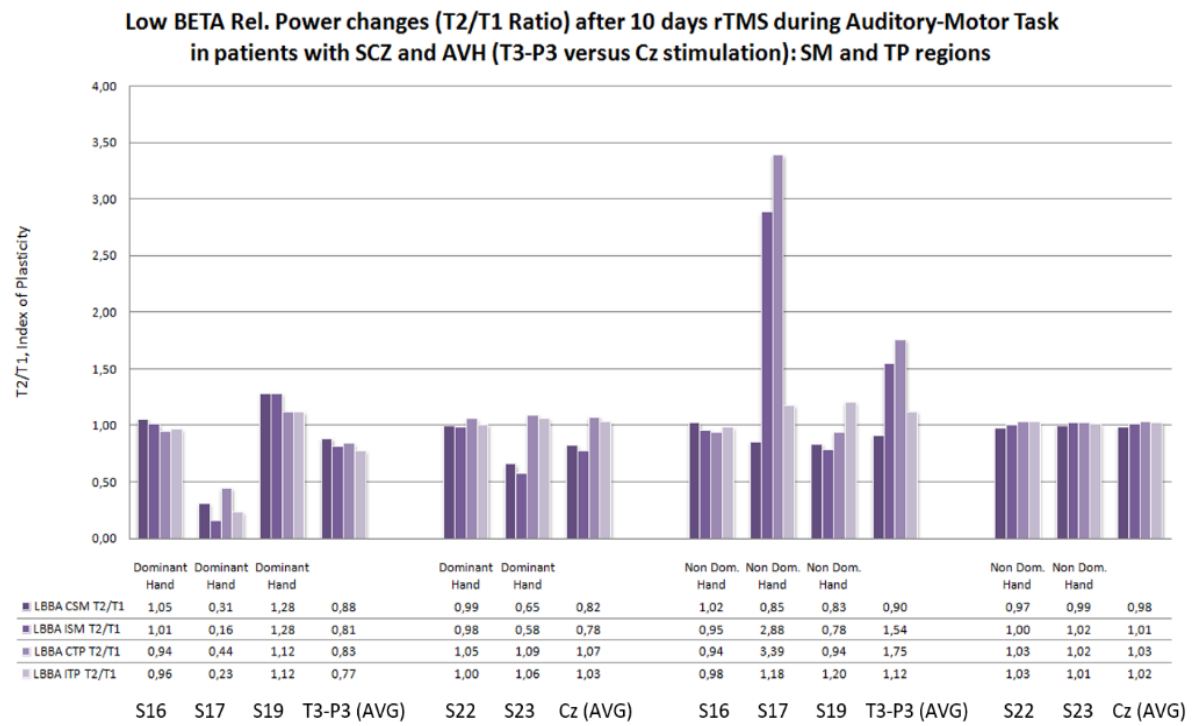


Figure 4-21 *Low Beta band activity changes during AM task.*

Gamma activity index of plasticity (during MCA epoch including *Bereitschaftspotential* period) showed maximum changes over all the ROI, especially over the ipsilateral sensorimotor cortex when the task was performed with the dominant hand (**Figure 4-24**).

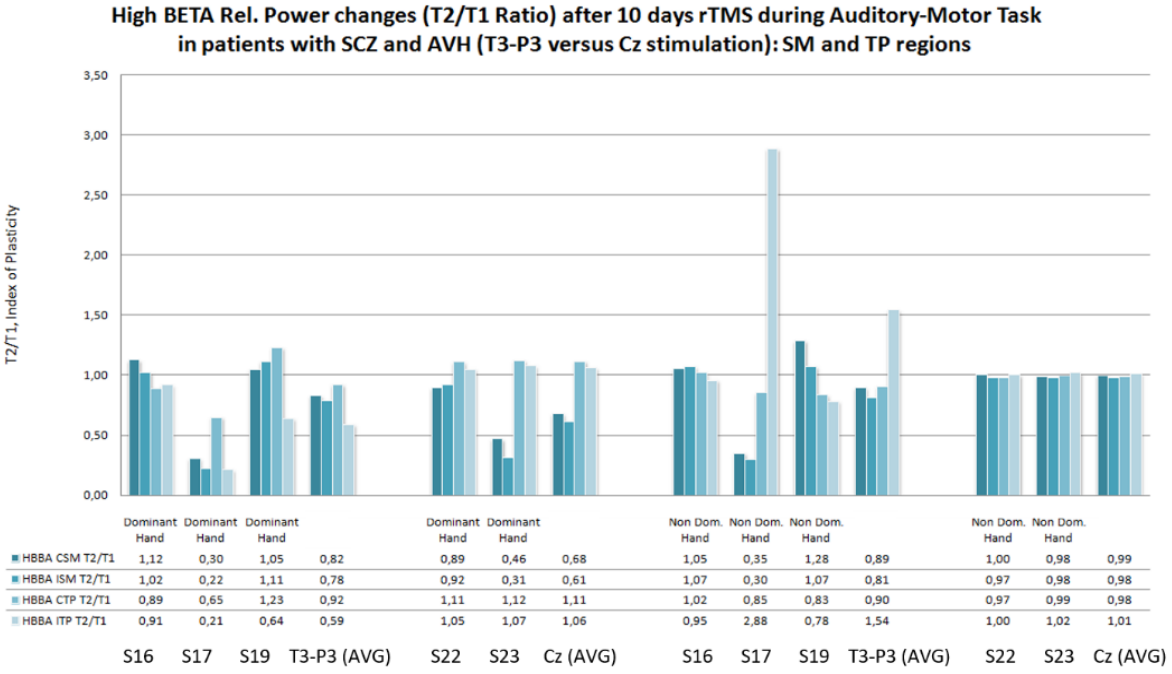


Figure 4-23 *High Beta band activity changes during AM task.*

Conclusions

The patients showed inter-subject and inter-group variability when we analyzed the relative power changes after 10 days of RTMS. Even so, we observed that beta activity

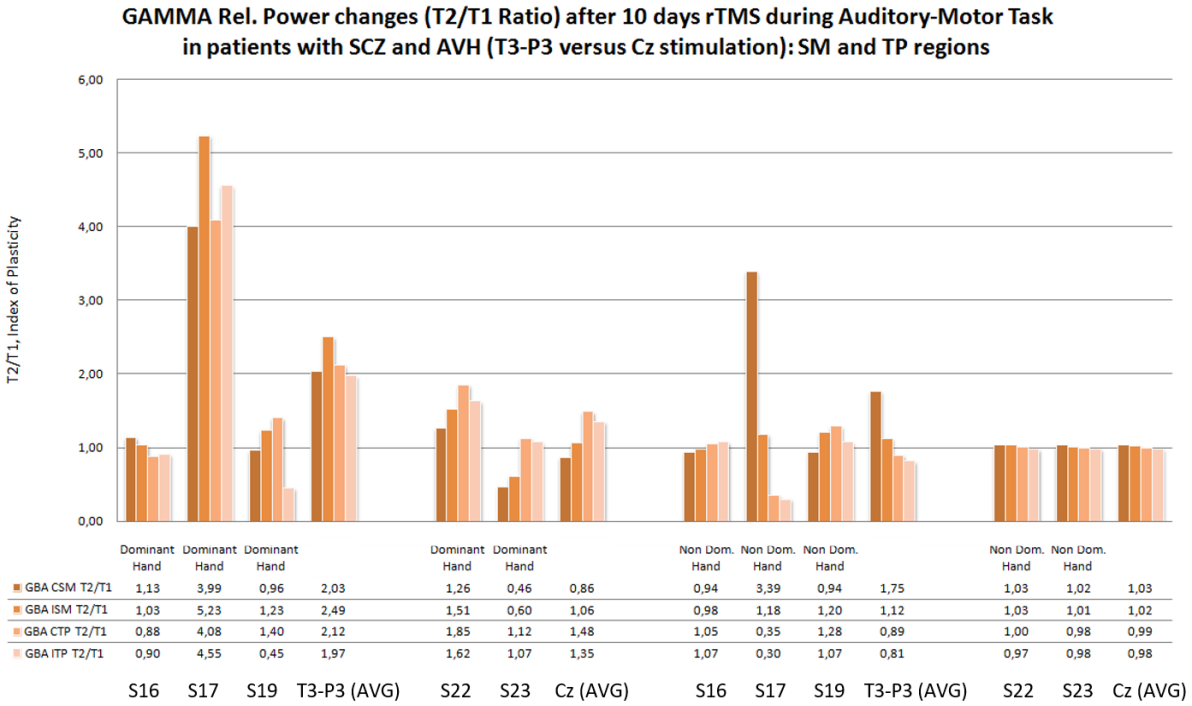


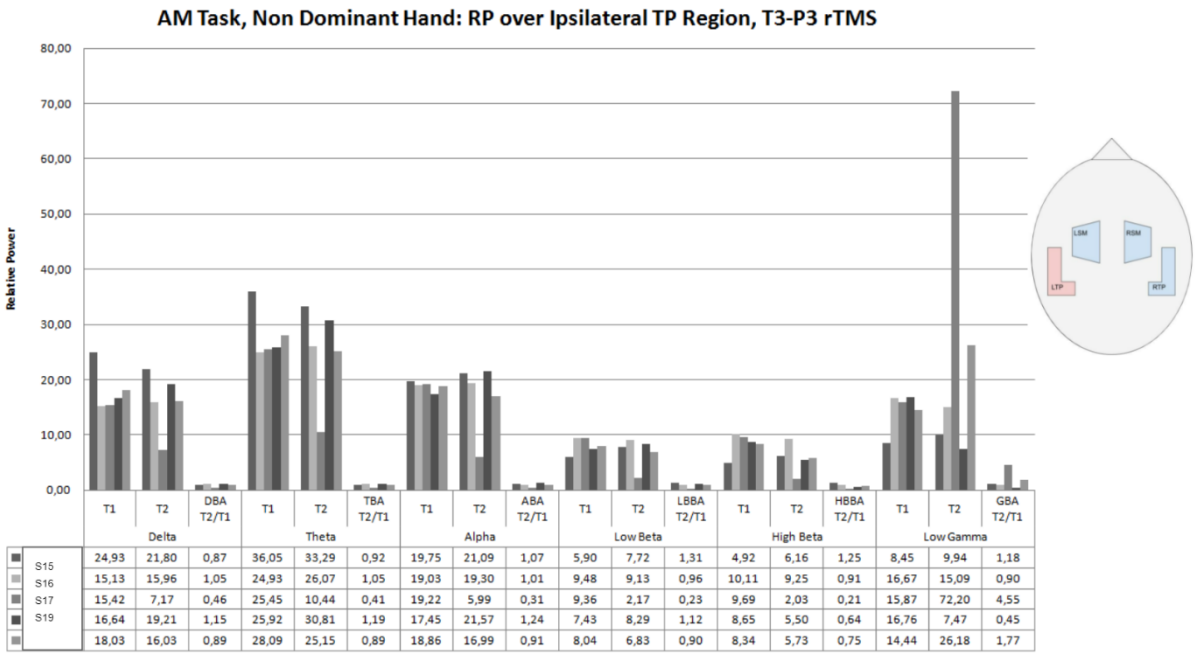
Figure 4-24 *Gamma band activity changes during AM task.*

measured with T2/T1 index showed major changes after RTMS over ipsilateral sensorimotor cortex when the AM task was performed with the non-dominant hand while gamma activity

changes were more sensitive to the dominant hand in all regions. This study has serious limitations like sample size and the different medications which might have interfered with the physiological responses.

Relative power EEG maps

Histogram graphs (**Figure 4-25**) were used to assess data distribution over the regions of interest and detect easier the local changes in relative power. "Bird-eye" view EEG maps were helpful to understand the changes in HS. Initially, we did not normalize the inter-subject data and we could observe the cortical distribution of EEG activity during MCA, ACA, or NCA epochs.



	T1	T2	DBA T2/T1	T1	T2	TBA T2/T1	T1	T2	ABA T2/T1	T1	T2	LBBA T2/T1	T1	T2	HBBA T2/T1	T1	T2	GBA T2/T1
	Delta			Theta			Alpha			Low Beta			High Beta			Low Gamma		
S15	24,93	21,80	0,87	36,05	33,29	0,92	19,75	21,09	1,07	5,90	7,72	1,31	4,92	6,16	1,25	8,45	9,94	1,18
S16	15,13	15,96	1,05	24,93	26,07	1,05	19,03	19,30	1,01	9,48	9,13	0,96	10,11	9,25	0,91	16,67	15,09	0,90
S17	15,42	7,17	0,46	25,45	10,44	0,41	19,22	5,99	0,31	9,36	2,17	0,23	9,69	2,03	0,21	15,87	72,20	4,55
S19	16,64	19,21	1,15	25,92	30,81	1,19	17,45	21,57	1,24	7,43	8,29	1,12	8,65	5,50	0,64	16,76	7,47	0,45
	18,03	16,03	0,89	28,09	25,15	0,89	18,86	16,99	0,91	8,04	6,83	0,90	8,34	5,73	0,75	14,44	26,18	1,77

Figure 4-25 *Changes of Relative Power, locally. Subject S17 showed increased gamma activity over left temporoparietal region, GBA Index = 4,55. The last raw, showed AVG data.*

The relative power (RP) is derived by expressing absolute power in each frequency band as a percent of the absolute power (AP) summed over all frequency bands (Yuvaraj et al., 2014b). RP calculation was performed in MATLAB (**Figure 4-26**).

```
Relative Power (myRP.m)

function RP=myRP(psd,f)
idxTOT=(find(f==8): find(f==100));
bands=[8,13,30,49,100];
Ptot=trapz(psd(:,idxTOT),2);
P= zeros(size(psd,1),4);

for i=1:4
    idx=(find(f==bands(i)):find(f==bands(i+1)));
    P(:,i)=trapz(psd(:,idx),2);
end

RP=100*P./repmat (Ptot,1,4);
```

Figure 4-26 *Relative power function used during the work-up of EEG data*

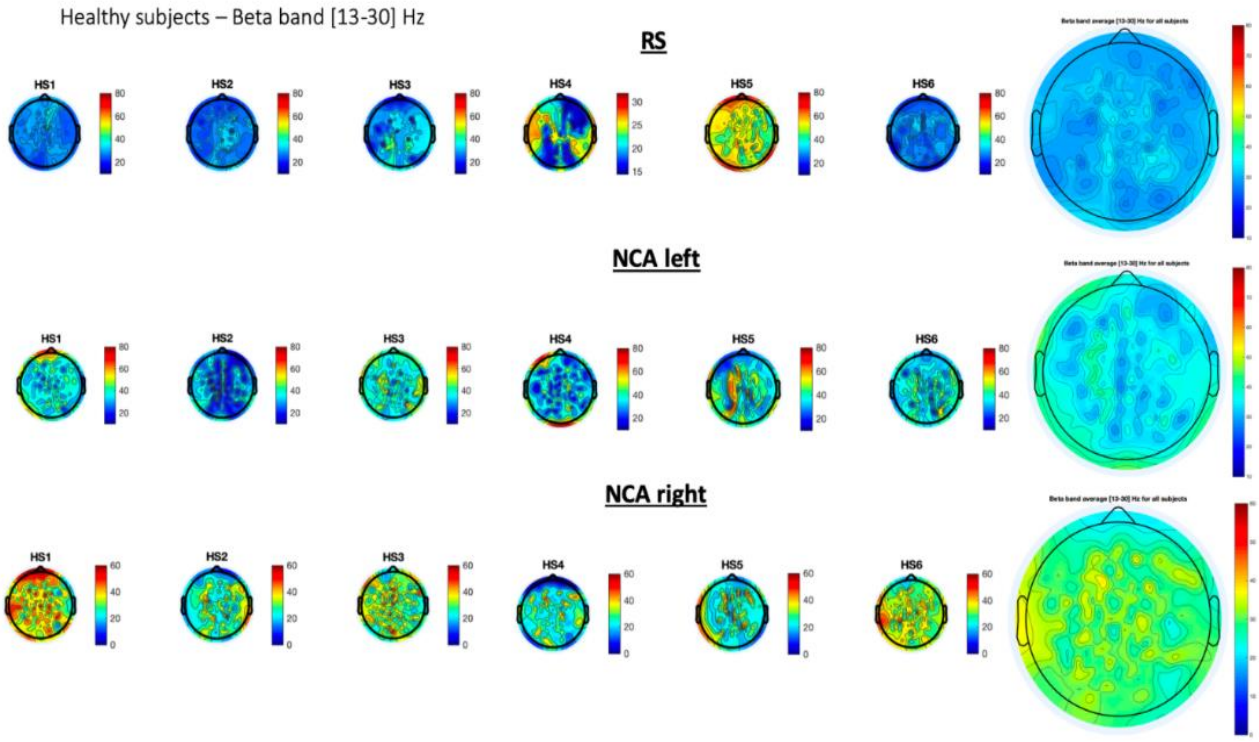


Figure 4-27 *HS (n6) showed increased beta band activity during the working memory related epoch, NCA, when the task is performed with the Dominant Hand. Data is not normalized. 2021 © S Marcu & OC Banea, Neurophysiology Plus*

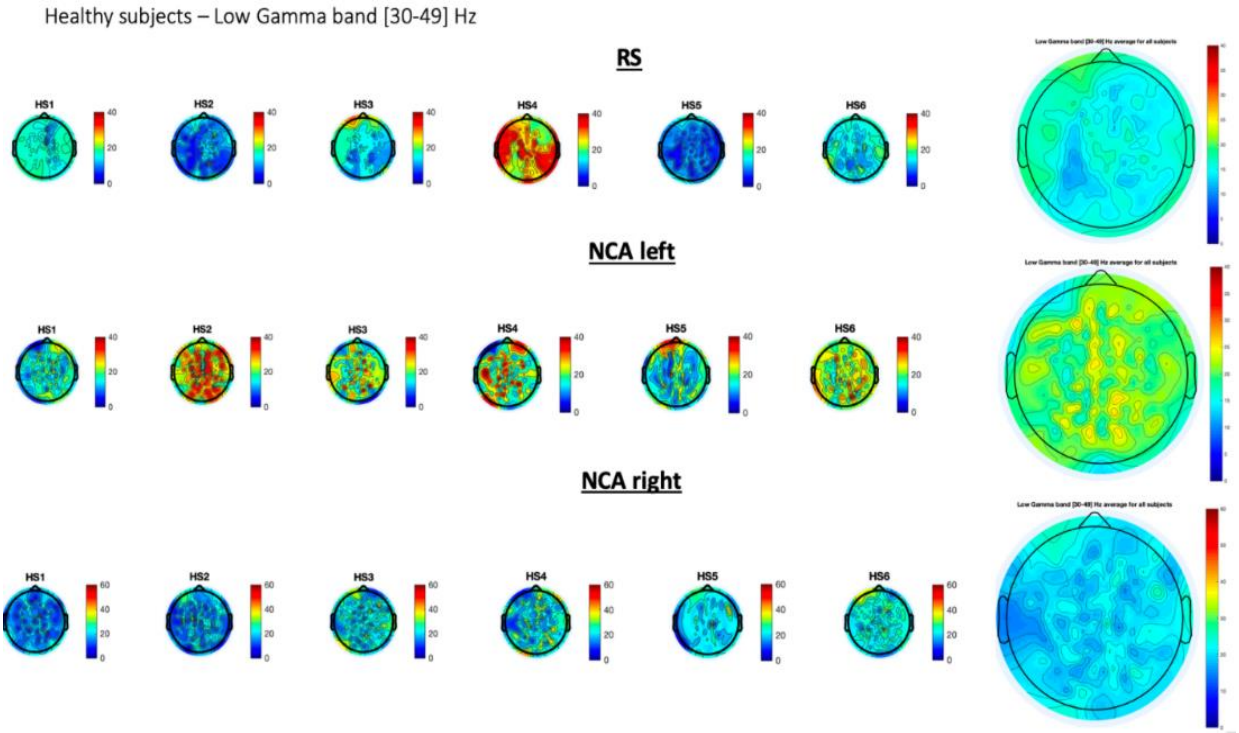


Figure 4-28 *HS (n6) showed higher low gamma-band activity during the working memory-related epoch, NCA, when the task is performed with the Non-dominant Hand. Data is not normalized. 2021 © S Marcu & OC Banea, Neurophysiology Plus*

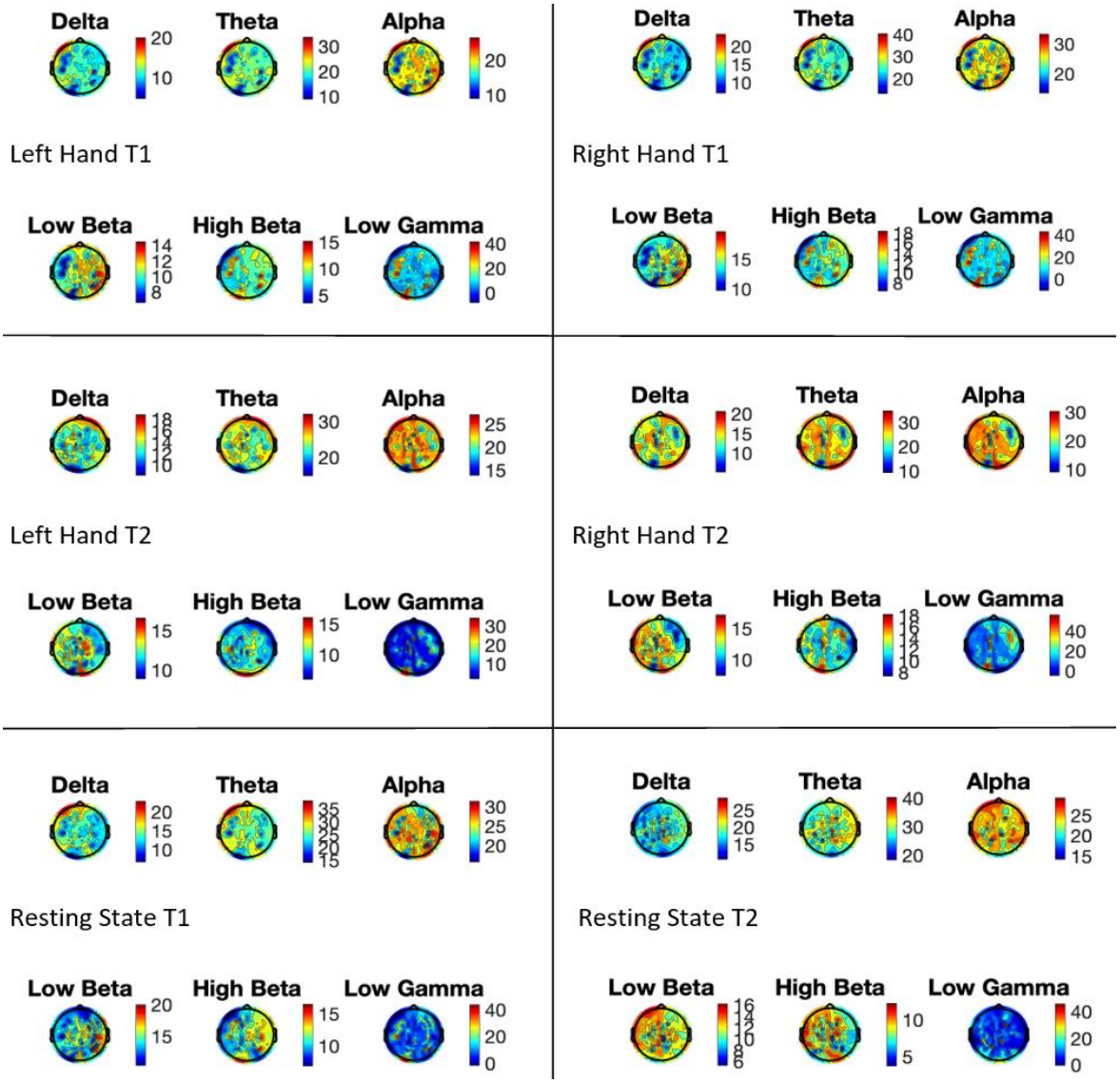


Figure 4-29 *RTMS effects on "bird-eye" view maps (relative power) during NCA of the AMT and RS in a patient with SCZ*

Power spectral density during auditory-motor task

PSD ($\mu V^2/Hz$) is performed with different windowing methods and is a type of spectral analysis. Data derived from PSD T2/T1 index was used to visualize inter-subject variability in six regions of interest, which are related to the auditory-motor brain network regions.

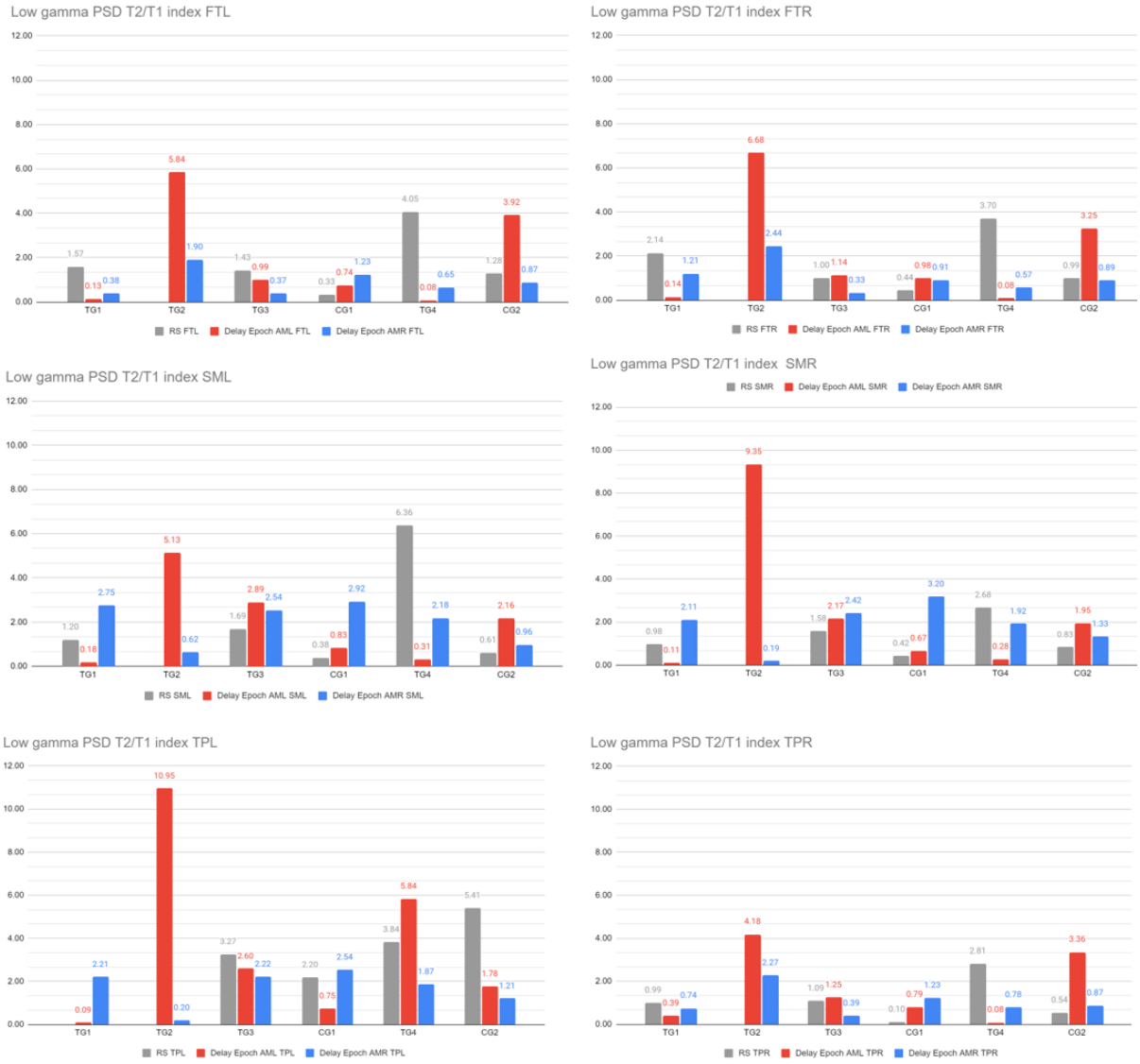


Figure 4-30 *PSD T2/T1 index during resting state (grey), AMT-left (red) and AMT-right (blue) obtained from 6 ROI. TG1=S16, TG2=S17, TG3=S19, CG1=S23 and CG2=S22. An index > 1 represents increment of PSD and <1 represents decrement of PSD activity.*

4.3.2 Methods

Subjects

For this work, we included subjects from both groups (TG and CG), and they were analyzed before (SCZ-T1) and after RTMS (SCZ-T2). Six patients (mean age = 30.2, SD 2.9, 5 males and 1 female) diagnosed with schizophrenia following the ICD-10 schizophrenia classification (F20) (SCZ group) and six healthy controls (HC) (mean age = 28.7, SD 4.3, 4 males and 2 females) participated in this study. The patients were recruited from the psychiatric wards and outpatient clinics at the National Hospital. The following inclusion criteria were applied to recruit SCZ patients: 1) age between 18 and 60-year-old, 2) refractory AVH due to schizophrenia or schizoaffective disorder for at least 1 year, and 3) presence of daily verbal hallucinations. Refractory AVH symptoms refer to two pharmacotherapy attempts with the

recommended dosage for at least 6-8 weeks. Moreover, the following exclusion criteria were applied: 1) history of epilepsy; 2) daily cannabis use; 3) use of other hard drugs within one month before the study or during the study; 4) alcohol abuse for more than three units of alcohol daily; 5) use of benzodiazepine daily or antiepileptic agents; and 6) meet any of the exclusion criteria on the TMS safety (Rossi et al., 2021). The study was approved by the Health Research Ethics Committee of Landspítali University Hospital (Approval No 21. 2018).

Auditory motor task

The AMT task was employed in a sound-attenuated room, and each patient was awake, un-sedated, and comfortably seated on a chair during the tasks. Subjects held a button in one hand and placed the hand on the thigh. We instructed each subject to press the button using the thumb when the pre-recorded verbal command "press" was given and not to press the button when the verbal command "no press" was given (**Figure 4-31**, C). Subsequently, each subject completed two auditory-motor tasks (one for each hand). The AMT task contained 40 trials: 20 auditory verbal "press" commands and 20 "no press" commands. The interstimulus interval was 3 seconds (Nagasawa et al., 2010). The commands were presented in a pseudorandom sequence during each task. The AMT was performed with the dominant hand (AMT-r), and non-dominant hand (AMT-l) one time in HC and two times in the SCZ group, before the RTMS treatment (T1) and within one week after completing ten sessions of RTMS treatment (T2).

EEG preprocessing

The raw EEG data of the three different files, RS, AMT-l, and AMT-r were imported for each subject. Channels were located and the sample rate was set at 256 Hz. A bandpass 1-100 Hz filter and 49-51 Hz notch filter were applied, followed by common average re-reference. Artifacts were classified with Independent Component Analysis (ICA) and bad components were semi-automatically excluded using ICLabel (Pion-Tonachini et al., 2019) and SASICA algorithms. For the AMT we defined three epochs in the time-series continuous data as follows: 1) delay epoch (DE) between -2.5 to -1.5 seconds before "press" and "no press" triggers (Peled et al., 2001); 2) auditory cortical activation (ACA) epoch, from 0 to 500 ms relative to the triggers "press" and "no press"; and 3) motor cortical activation (MCA) epoch, between 0 and 500 ms relative to the button "press" (hand reaction code). All epochs and trials were corrected using 200 ms of baseline.

Regions of interest

Working memory (WM) deficits are related to ventromedial prefrontal - parietal control deactivation (Eryilmaz et al., 2016), frontoparietal connectivity dysfunction (Nielsen et al., 2017), or lack of frontotemporal activations (Peled et al., 2001). The change of beta and gamma synchronization during auditory-motor tasks was previously described over supratemporal and sensorimotor gyri (Nagasawa et al., 2010). Based on these previous studies, we selected six regions of interest (ROI) involved in auditory-motor integration to observe the network organization at the cortical level. Each ROI is represented by 17 electrodes. The total number of electrodes was 102 (6 x 17 sensors). The ROIs were selected using MATLAB script as follows: left frontal (LF), left sensorimotor (LSM), left temporoparietal (LTP), right frontal (RF), right sensorimotor (RSM), and right temporoparietal (RTP) (**Figure 4-31**, E).

Outcomes

Clinical symptoms were used as primary outcomes (QoL, DASS, and PSYRATS AHS). Additionally, we measured power spectral density and network organization using graph theory algorithms as secondary neurophysiological outcomes.

Electrophysiological outcome

The power spectral density (PSD) was calculated for each subject in those electrodes that were classified as good, by performing Fast Fourier Transform (FFT)-based analysis using Welch's method with 250 ms Hamming window and 50% overlap. The estimation of PSD was carried out by dividing the time signal into (overlapping) subsequences, forming the periodogram for each subsequence, and averaging. Relative power was then computed for the following frequency bands of interest: alpha (8–13 Hz), beta (13–30 Hz), low gamma (30–49 Hz), and high gamma (51–100 Hz). The units of PSD are micro-Volts-squared per Hz (uV2/Hz).

To describe the network organization using graph-theory algorithms, we calculated the Magnitude Squared Coherence (MSC) between each possible pair of ROIs electrodes into the DE, ACA, and MCA epochs to measure the undirected phase connectivity between the electrodes for each subject (Equation 1). We used a 250 ms Hamming window with 90% overlap for each pairwise measure that results in a 102 x 102 connectivity matrix containing all values among the six predefined ROIs.

$$MSC(f) = \frac{|Pxy(f)|^2}{Pxx(f)Pyy(f)} \qquad (1)$$

A threshold was applied after the creation of the connectivity matrices to remove the connections above and below 0.5 standard deviations of the average MSC of the entire matrix, resulting in significant values that represent the average activity of the scalp network. The significant matrices were then transformed in a directed graph (G) composed of vertices V(G), edges E(G), and weights. The electrodes represent nodes (or vertex), and the connections between phase connectivity measured by MSC represent the edges. The complex dynamic of the scalp network was described using the following variables: number of nodes, number of edges, mean degree centrality, clustering coefficient (Equation 2), characteristic path length (Equation 3), and small-worldness (Equation 4).

The clustering coefficient measures the local clustering coefficients of all the vertices:

$$C = \frac{1}{n}\sum_{i \in N} \frac{2t_i}{k_i(k_i-1)} \qquad (2)$$

k_i represents all connected neighbors to node i

t_i represents the number of links between them.

The characteristic path length (L) is a measure of the efficiency of connection among nodes. It is measured by the average shortest path length between all pairs of nodes:

$$L = \frac{1}{n(n-1)} \sum_{i \neq j} d(v_i, v_j) \qquad (3)$$

n represents the number of vertices of a Graph.

The small-worldness (SM) measures directly the randomness of a complex network. The SM index is calculated by the clustering coefficient (C) and the characteristic path length (L) ratio by size-matched L/L(random) network (Watts & Strogatz, 1998):

$$SW = \frac{C \,/\, C_{rand}}{L \,/\, L_{rand}} \qquad (4)$$

Statistics

Descriptive statistics are based on median and standard deviation per group and variable. Kruskal-Wallis nonparametric for non-normal data and Two-Way Mixed ANOVA for normal distributed variables tests were performed in each ROI and frequency bands considering the three groups (HC, SCZ-T1, and SCZ-T2) as independent variables. Wilcoxon paired tests were applied as post hoc with a corrected p-value for multiple comparisons in those significantly different frequencies and ROIs for PSD analysis. Dunn's post hoc tests were applied within each group in the network analysis. Non-parametric Kendall's tau-b correlation was also applied to describe the relationships between EEG (PSD or connectivity with graphs) variables and psychometric scales before and after the RTMS protocol. Differences were significant if the corrected p-value was < 0.05.

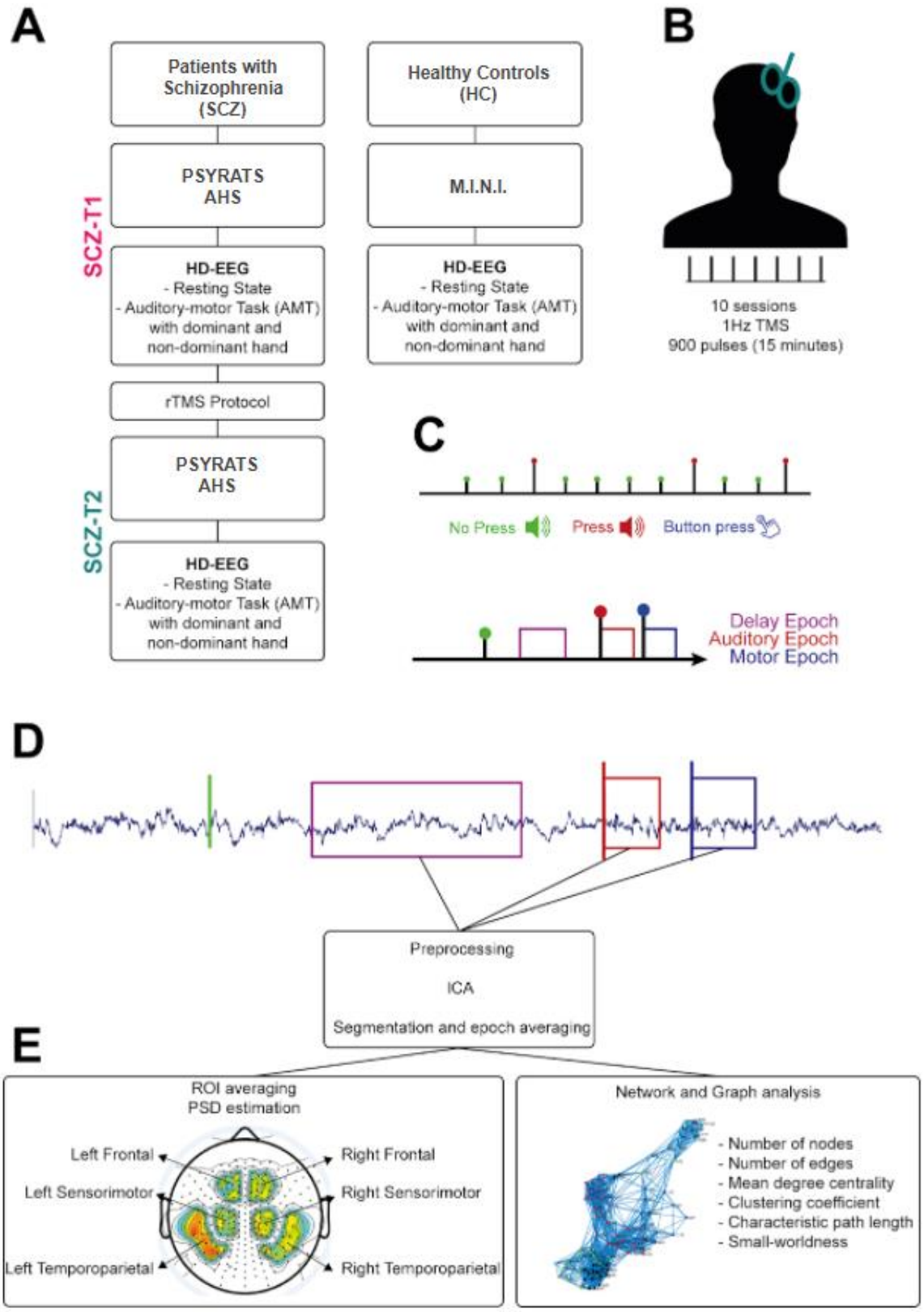


Figure 4-31 *Protocol design. Study 5*

4.3.3 Results

Effects of RTMS on psychotic symptoms

A one-way repeated subject ANOVA showed a significant improvement on psychotic symptoms as measured by PSYRATS between pre - RTMS (M = 28,6, Std = 4,17) and post - RTMS (M = 23,6, std = 5,27) conditions, F (1, 5) = 23,44, p < 0,05, ηp^2 = 0,967 (**Figure 4-32**).

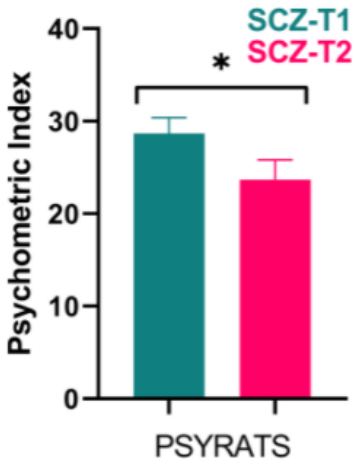


Figure 4-32 *RTMS changed PSYRATS AHS score at a significant level*

PSD during resting-state EEG, T1 and T2

Over the left sensorimotor ROI, we found differences in the gamma spectrum, specifically in Low-gamma (30-49 Hz) and High-gamma (51-100 Hz) oscillations. In detail, SCZ patients showed increased Low-gamma power in both SCZ-T1 (Med = 0.2, Std = 0.16) and SCZ-T2 (Med = 0.16, Std = 0.023), when compared with HC power (Med = 0.029, Std = 0.013). Kruskal-Wallis test showed an effect size of χ^2 (2) = 7.71, p = 0.021, with a mean rank pain score of 3.60 for HC, 10.60 for SCZ-T1 and 10.83 for SCZ-T2. Post hoc showed significant differences between HC and SCZ-T1 (W = 16, p = 0.016) and between HC and SCZ-T2 (W = 15, p < 0.01). We also observed the same trend in the high-gamma spectrum in the three groups: SCZ-T1 (Med = 0.19, Std = 0.16), SCZ-T2 (Med = 0.17, Std = 0.18) and HC (Med = 0.016, Std = 0.017). The Kruskal-Wallis H test showed a difference in high-gamma PSD within left sensorimotor region χ^2 (2) = 9.05, p = 0.011, with a mean rank pain score of 3.20 for HC, 10.60 for SCZ-T1 and 10.17 for SCZ-T2. Post hoc indicated that both SCZ-T1 (W = 18, p = 0.05) and SCZ-T2 (W = 17, p = 0.017) are different from HC subjects. No significant differences were found between SCZ-T1 and SCZ-T2 in Low and High-gamma bandwidths (p > 0.05).

SCZ patients also showed increased High-gamma (51-100 Hz) over the right sensorimotor ROI [SCZ-T1(Med = 0.12, Std = 0.07); SCZ-T2(Med = 0.11, Std = 0.022); HC (Med = 0.013, Std = 0.019)]. Kruskal-Wallis H test showed differences between groups (χ^2 (2) = 6.5, p = 0.03) with a mean rank pain score of 4.0 for HC, 10.20 for SCZ-T1 and 10.33 for SCZ-T2. Post hoc Wilcoxon test indicated differences only between HC and SCZ-T2 (W = 17; p = 0.017).

Low-gamma (30-49 Hz) oscillations were increased in SCZ patients regardless of RTMS protocol over the left temporoparietal cortex [SCZ-T1(Med = 0.08, Std = 0.11); SCZ-T2(Med = 0.23, Std = 0.15); HC (Med = 0.018, Std = 0.04)]. Kruskal-Wallis H confirmed a main effect between groups (χ^2 (2) = 6.62, p = 0.036) with a mean rank pain score of 4.40 for HC, 7.5 for SCZ-T1 and 11.3 for SCZ-T2. Corroborating with the right sensorimotor activity, low-gamma spectrum showed difference between HC and SCZ-T2 (W = 17; p = 0.017), suggesting a RTMS modulation over this region in SCZ patients.

Moreover, high-gamma oscillations seem to be a hallmark of RTMS in SCZ-T2 in both

frontal regions. In detail, Kruskal-Wallis H test confirmed a main difference over the left (χ^2 (2) = 7.7, p = 0.021) and right (χ^2 (2) = 7.91, p = 0.019) frontal ROIs. Post hoc Wilcoxon W test confirmed the effect between HC and SCZ-T2 in left (U = 15; p < 0.01) and right (U = 16; p < 0.01) frontal ROIs, respectively (**Figure 4-33**).

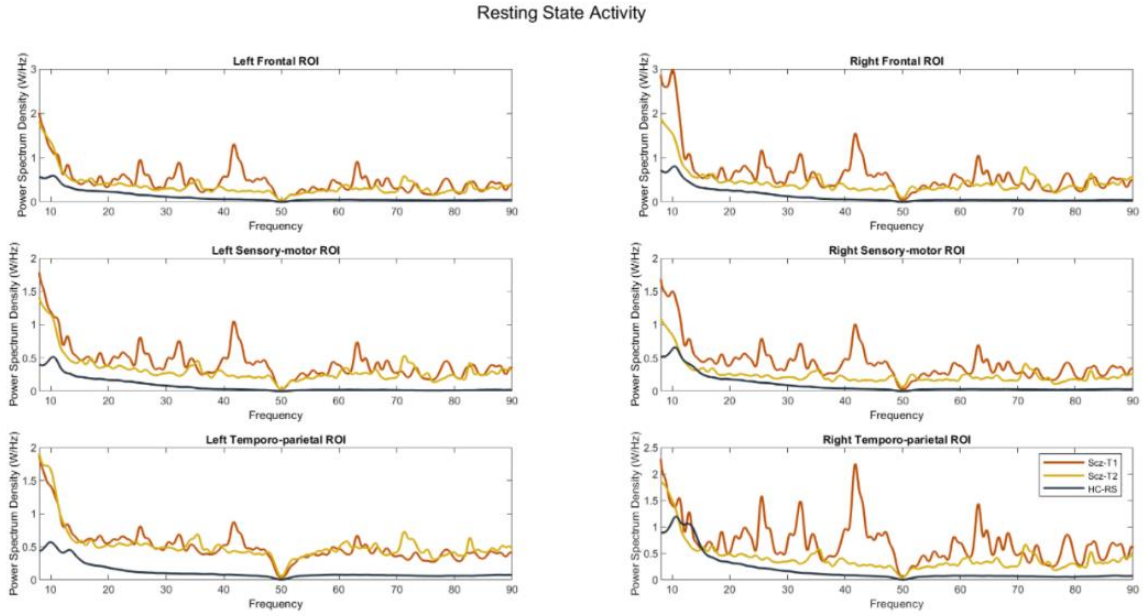


Figure 4-33 *PSD during resting state, T1 and T2 (AVG 6 SCZ and AVG 6 HS). SCZ T1 (brown), SCZ T2 (yellow), HS (black). Low-gamma band showed lowest PSD over the left temporoparietal region in SCZ T1 (bottom left). Copyright 2020 © LG Bandeira Dos Santos & OC Banea, Neurophysiology Plus Iceland*

PSD during auditory-motor task EEG (T1 and T2)

We analyzed the same parameters for all ROIs and groups in the EEG recordings performed consecutively with the behavioral auditory-motor task. ACA and MCA windows of interest did not show significant differences between groups when PSD was analyzed for all regions and conditions. Interestingly, patients showed a significant difference in both gamma oscillations over left temporoparietal ROI within NCA or "delay epoch" (Peled et al., 2001) (Table 1). Post hoc analysis showed the same pattern observed in resting-state recordings, with a difference only between HC and SCZ-T2 (W = 24, p = 0.01).

*Table 9 PSD (NCA) of Low and High gamma EEG activity changes after RTMS. * = Rank Pain Score, ** = Post Hoc Analysis*

Auditory-motor task, Non-Dominant Hand, Left Temporoparietal Region (T3-P3), Reference Period (Delay Epoch or NCA)								
EEG Band / Group	HC*	SCZ T1*	SCZ T2*	HC, SCZ T1, SCZ T2	HC vs SCZ T1 **	HC vs SCZ T2**	SCZ T1 vs SCZ T2**
PSD Low Gamma	5,33	10,17	**13**	χ^2 (2) = 6.32, p = 0.04		W:24, p:0,01	p > 0,05
PSD High Gamma	5	9,67	**13,83**	χ^2 (2) = 8.22, p = 0.016		W:21, p < 0,01	p > 0,05

High-gamma power also exhibits a similar pattern over the left temporoparietal ROI (Table 7) (χ^2 (2) = 8.22, p = 0.016) with a mean rank pain score of 5 for HC, 9.67 for SCZ-T1and 13.83 for SCZ-T2. Post hoc confirms a unique pairwise difference between HC and SCZ-T2 (W = 21, p < 0.01). The different epochs of the auditory-motor task showed clear differences of PSD interhemispheric laterality depending on the hand involved in the task.

MCA epoch (**Figure 4-34**) showed higher PSD in all regions during baseline (T1) when the task was performed with the non-dominant hand and from the left temporoparietal region when the task was performed with the ipsilateral hand. In T2, beta and gamma activity from

left temporoparietal ROI showed similar behavior as that for the HC group when the task was performed with the dominant hand.

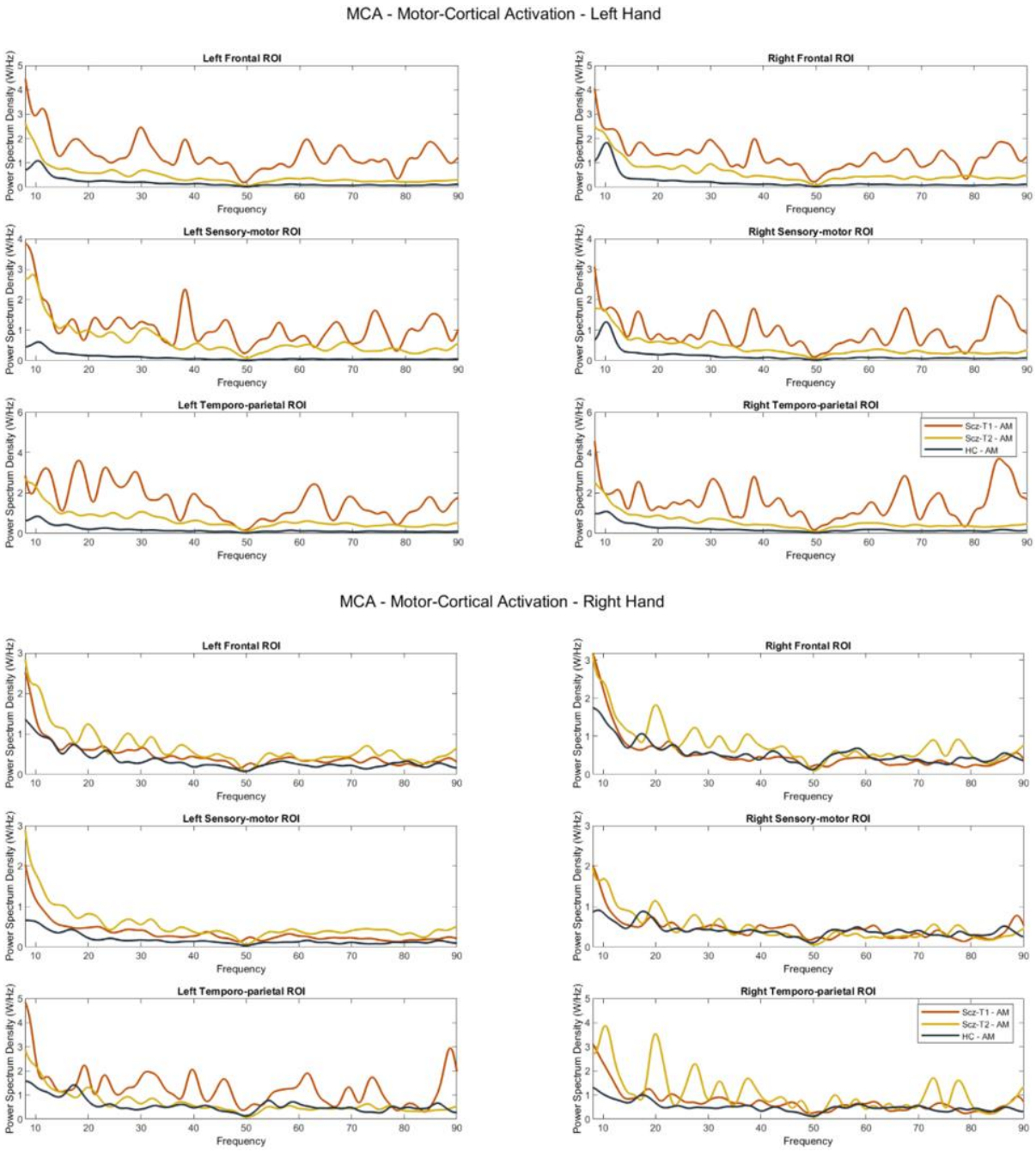


Figure 4-34 *PSD during MCA epoch from both frontal (upper figures), sensory-motor (figures in the middle row), and temporoparietal (lower figures) ROI. 8-90Hz. Non-dominant (Top). Copyright 2020 © LG Bandeira Dos Santos & OC Banea*

During the epoch of ACA, PSD interhemispheric laterality showed similar responses to the MCA epoch with higher values obtained in all ROI while the task was done with the non-dominant hand and over the left temporoparietal region when the dominant hand was used for the task (**Figure 4-35**).

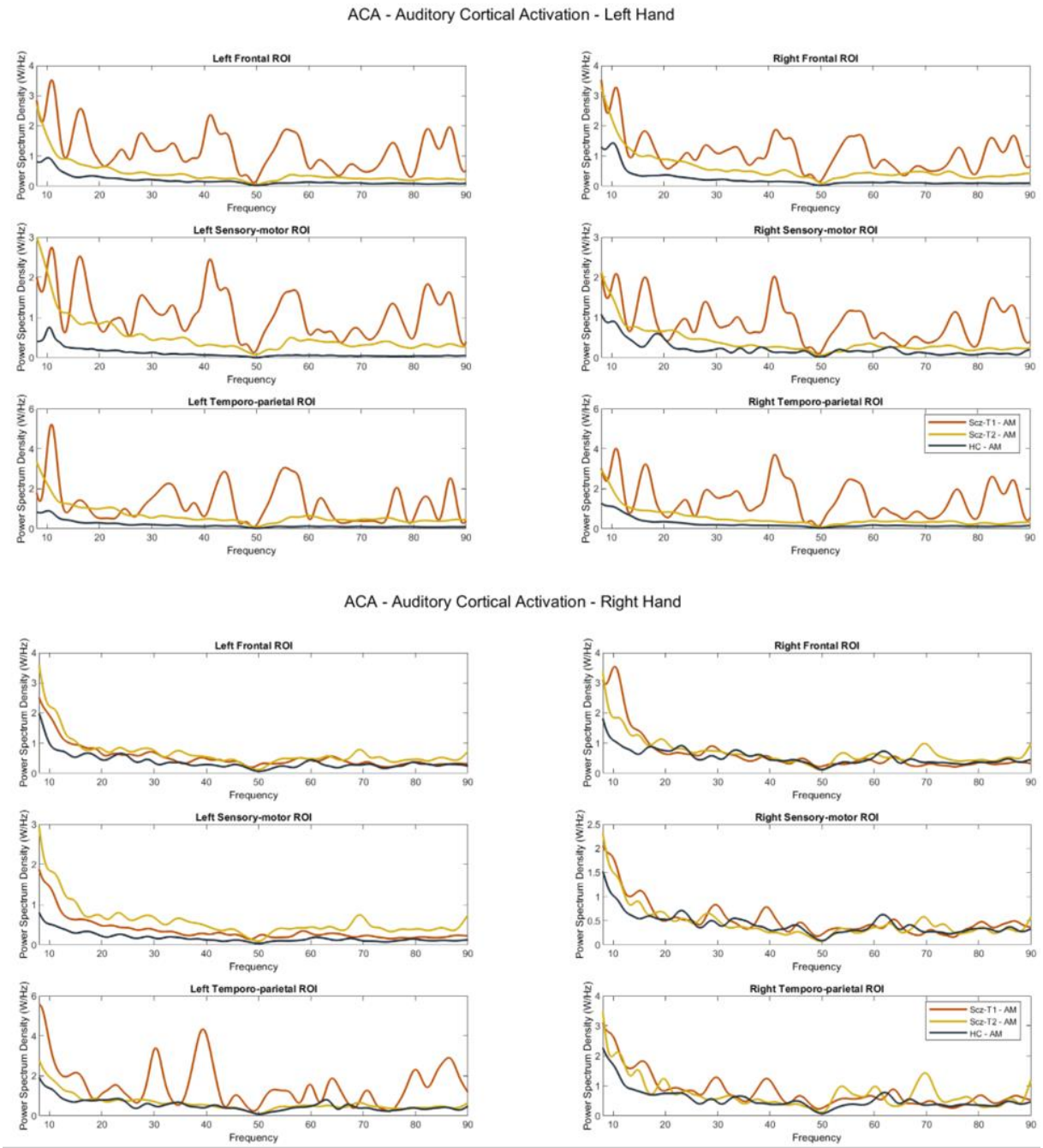


Figure 4-35 *PSD during ACA epoch from both frontal (upper figures), sensory-motor (figures in the middle row), and temporoparietal (lower figures) ROI. 8-90Hz. Non-dominant (Top). Copyright 2020 © LG Bandeira Dos Santos & OC Banea*

The NCA or "delay epoch", a period in between commands "Press" and "Do not press", which is related to the working memory (Peled et al., 2001), was the only one where the patients with schizophrenia showed higher low- and high-gamma PSD after RTMS (**Figure 4-36**). In the figure describing individual PSD T2/T1 index change, we could observe an increment of gamma activity up to 9 times for Patient S17 (**Figure 4-36**). This might be outlined data that can produce bias to this graphic representation.

Therefore, another method is needed to assess the connectivity degree of the anatomical regions involved in the auditory-motor task.

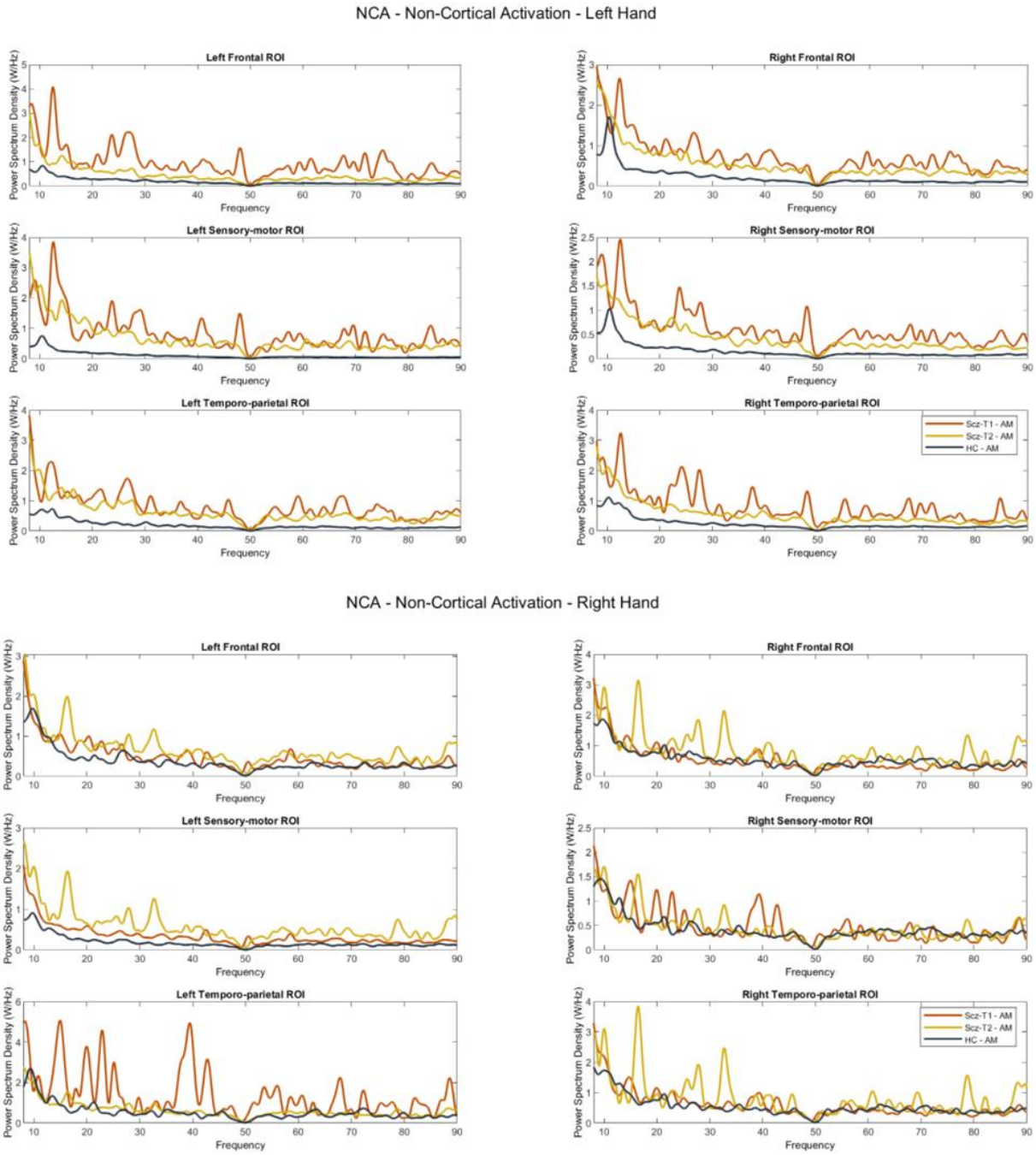


Figure 4-36 *PSD during NCA epoch from both frontal (upper figures), sensory-motor (figures in the middle row), and temporoparietal (lower figures) ROI. 8-90Hz. Non-dominant (Top). Copyright 2020 © LG Bandeira Dos Santos & OC Banea*

Network organization

To characterize the whole-scalp connectivity through graph-based networks, we applied pair-wise Magnitude Squared Coherence (MSC) on each possible pair of connections between the electrodes participating in the determined ROIs for the RS, AMT-r, and AMT-l. The MCS estimate is a function of frequency with values between 0 and 1. These values indicate how well PSD calculated for the electrode *x* corresponds to PSD of electrode *y* at each frequency. The ***magnitude-squared coherence*** is a *function* of the power spectral densities, P*xx*(*f*) and P*yy*(*f*), and the cross power spectral density, P*xy*(*f*), of *x* and *y* (see in *Methods*). The network organization is then "calculated" with the metrics of the graph constructed with adjacency

connectivity matrix done with cross power spectral density values (Figure 4-37).

The results described here are related to the "delay epoch" since the PSD results indicated differences only in this EEG recording window. ACA and MCA windows of interest did not show significant differences between groups when network organization was analyzed with graphs and SWN. Graph's theory networks of low gamma activity resulting from the NCA epoch of the auditory-motor task performed with the non-dominant hand is shown for two patients (one of each group), before (T1) and after the RTMS (T2) (**Figure 4-43**).

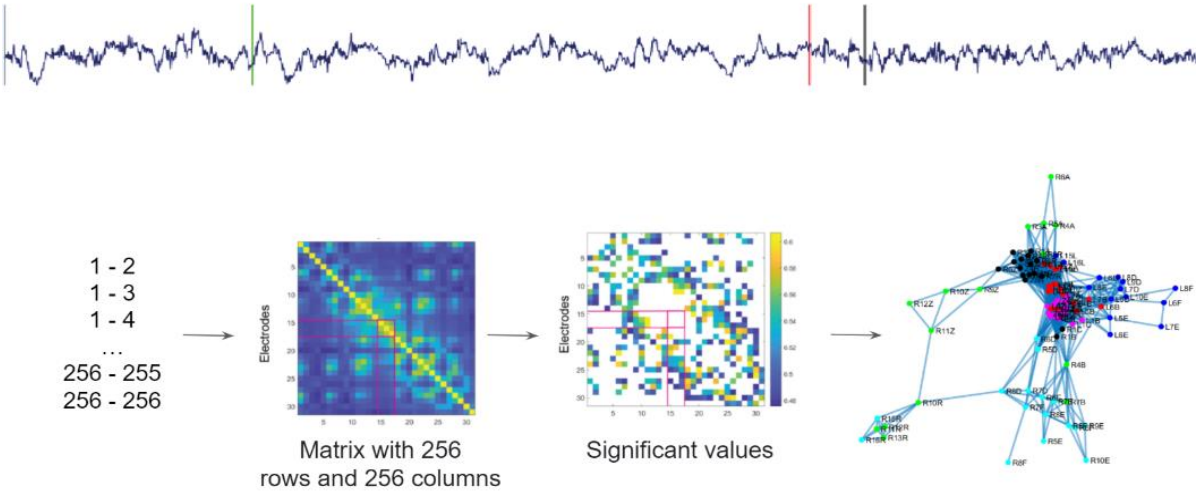


Figure 4-37 Network organization derived from cross power spectral density

Alpha networks

For Alpha (8-13 Hz) networks, Two-Way Mixed ANOVA showed that there was a significant main effect of the condition (RS, AMT-r, and AMT-l) in the characteristic path length ($F(1, 2) = 13.482$, $p < 0.01$, $\eta p^2 = .442$). Dunn's post hoc within each group with a corrected p-value for multiple comparisons showed differences between RS and AMT-l of HC ($p < 0.01$) (Figure 4-38).

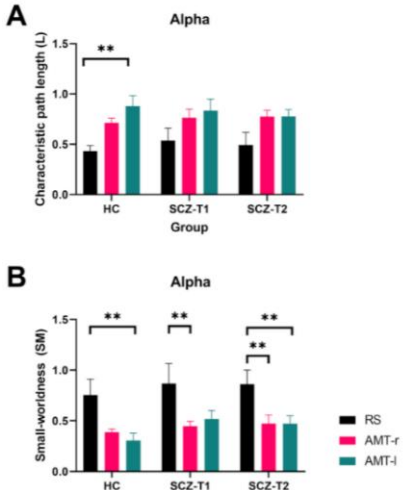


Figure 4-38 Alpha network Characteristic Path Length and SW index.

No differences were found among conditions in SCZ-T1 ($p > 0.05$) and SCZ-T2 ($p > 0.05$). We also found a main effect of the condition in the small-worldness scores ($F (1, 1.235) = 12.614$, $p < 0.01$, $\eta p^2 = .426$). Post hoc analysis showed interaction between RS and AMT-l within HC ($p > 0.02$) and SCZ-T2 ($p > 0.04$) groups. Surprisingly, SCZ patients significantly decreased the small-worldness of their alpha networks between RS and AMT-r (dominant hand) before ($p = 0.02$) and after ($p = .04$) the RTMS.

Beta networks

For Beta (13-30 Hz) networks, Two-Way Mixed ANOVA showed a significant main effect of the condition (RS, AMT-r and AMT-l) in characteristic path length ($F (1, 2) = 15.347$, $p < .01$, $\eta p^2 = .474$). Dunn's post hoc within each group with corrected p-value for multiple comparisons showed differences between RS and AMT-l in HC ($p < 0.01$) and RS and AMT-r after RTMS (SCZ-T2 group). We also found a main effect of condition in beta small-worldness ($F (1, 2) = 15.347$, $p < .01$, $\eta p^2 = .474$). Dunn's post hoc showed differences in RS and AMT-l of HC ($p < 0.043$) and SCZ-T2 ($p < 0.01$) groups. Patients after RTMS also exhibit lower small-worldness in AMT-r when compared with RS ($p < 0.001$) (Figure 4-39).

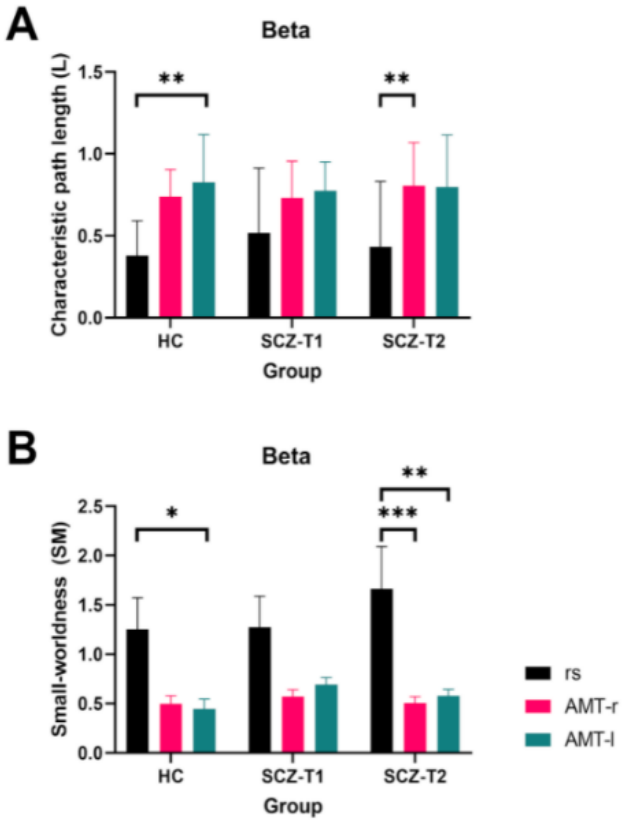


Figure 4-39 *Beta network Characteristic Path Length and SW index*

Gamma networks

For Low-gamma (30-49 Hz), Two-Way Mixed ANOVA showed a significant main effect of the condition (RS, AMT-r, and AMT-l) only in SW ($F (1, 1.037) = 10.774$, $p < 0.01$, $\eta p^2 = 0.388$). Dunn's post hoc within each group with a corrected p-value for multiple comparisons showed differences between RS and AMT-r and RS and AMT-l in HC ($p < 0.01$).

The same pattern was observed in SCZ patients in T2 ($p < 0.01$), suggesting that RTMS modulates the network and restores the randomicity of their networks at different conditions (RS, AMT-r, and AMT-l). High-gamma networks also showed a significant main effect of the condition (RS, AMT-r and AMT-l) only in SW ($F(1, 1.030) = 8.528$, $p < 0.01$, $\eta p^2 = 0.334$). Postdoc analysis showed that HC subjects exhibit different SW effects between RS and AMT-l ($p < 0.01$) and AMT-r ($p < 0.01$), however, this was not observed in SCZ-T2 patients, suggesting that RTMS modulates the small-worldness only in low-gamma networks (**Figure 4-40**).

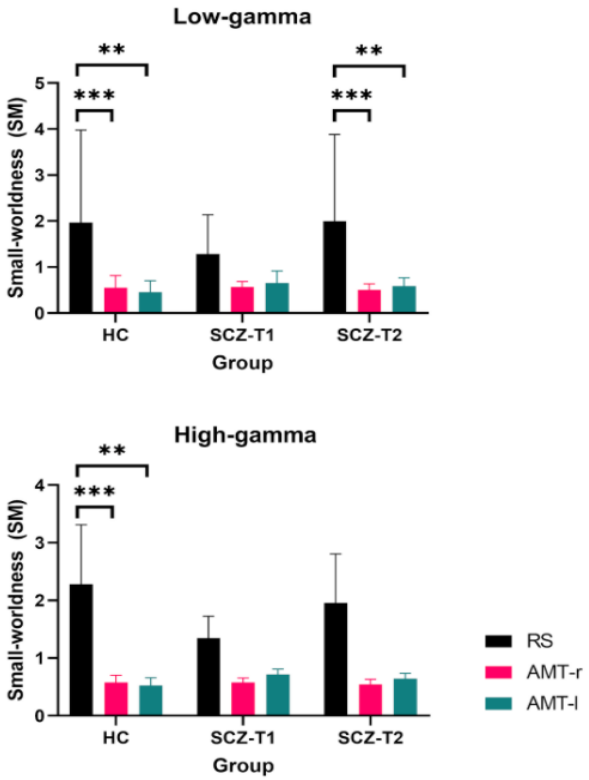


Figure 4-40 *Gamma network Characteristic Path Length and SW index*

Correlation between psychotic symptoms and small-worldness

After identifying that RTMS was able to show the same differences between the conditions in SCZ-T2 that resemble the HC group in low-gamma, we performed the Kendall's Tau correlation to investigate which of these conditions could be related to the improvement of psychotic symptoms after RTMS. Kendall's tau-b correlation showed a strong, negative correlation between the small-worldness of low-gamma phase oscillations of SCZ-T1 and PSYRATS scores, which was statistically significant ($\tau b = -0.788$, $p = 0.032$). On the other hand, Kendall's tau-b correlation showed a strong positive and significant correlation between the same measurements after RTMS (SCZ-T2 group), ($\tau b = 0.733$, $p = 0.039$). This result suggests that the small-world effect is correlated with the improvement of psychotic symptomatology after the RTMS in a different way than observed before RTMS (SCZ-T1 group), and furthermore, this can be a network signature in low-gamma of a possible treatment effect expressed through graph theory and EEG during an AMT performed with the non-

dominant hand (**Figure 4-42**).

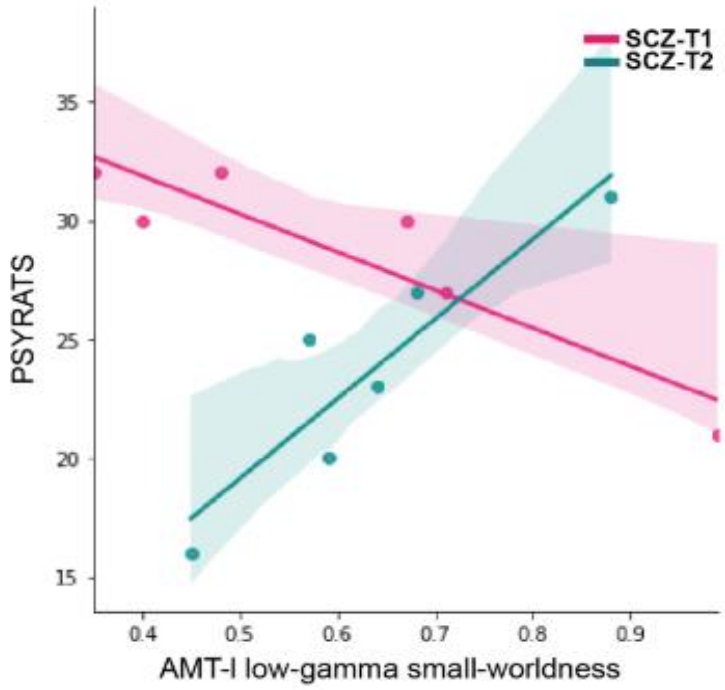


Figure 4-42 *Correlation between PSYRATS AHS and low-gamma small-world effect in patients with schizophrenia and AVH before (green) and after 10 days of RTMS (magenta). NCA of auditory-motor task with the non-dominant hand.*

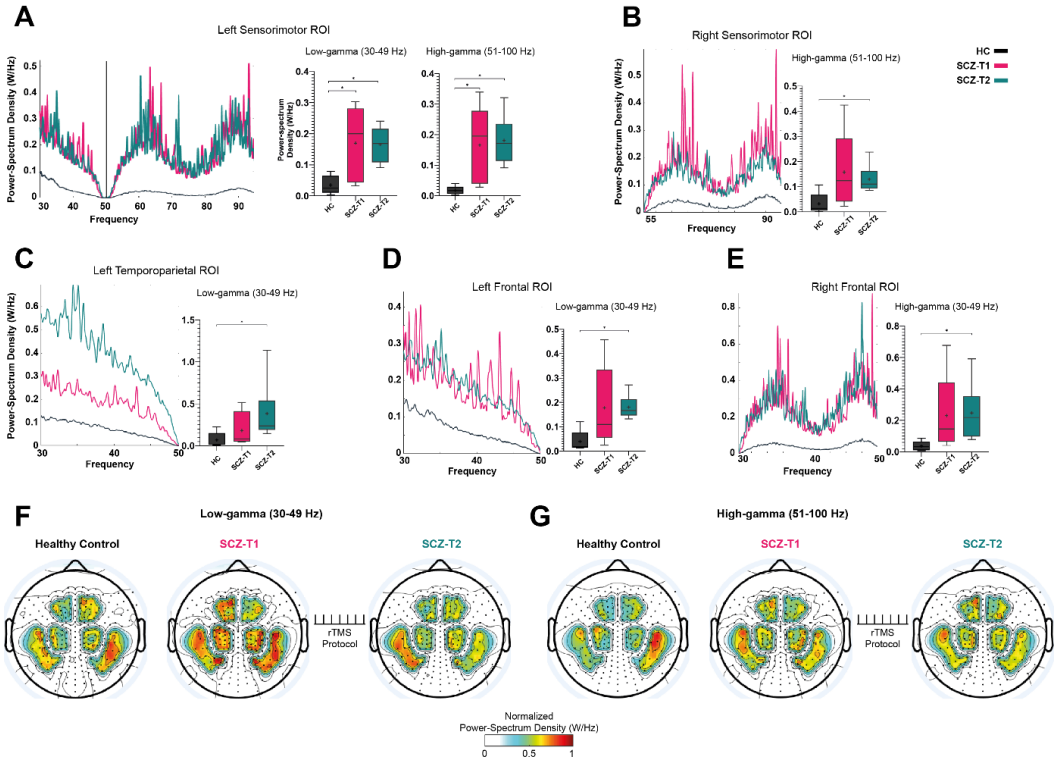


Figure 4-41 Resting state *of low and high gamma PSD with "bird-eye" view EEG maps (F and G). T1 (magenta) and T2 (green) PSD change in patients with SCZ compared with HC (black traces and boxplots). Sensory-motor ROI (A and B), frontal ROI (D and E). Low gamma PSD over left temporoparietal ROI increased after RTMS.*

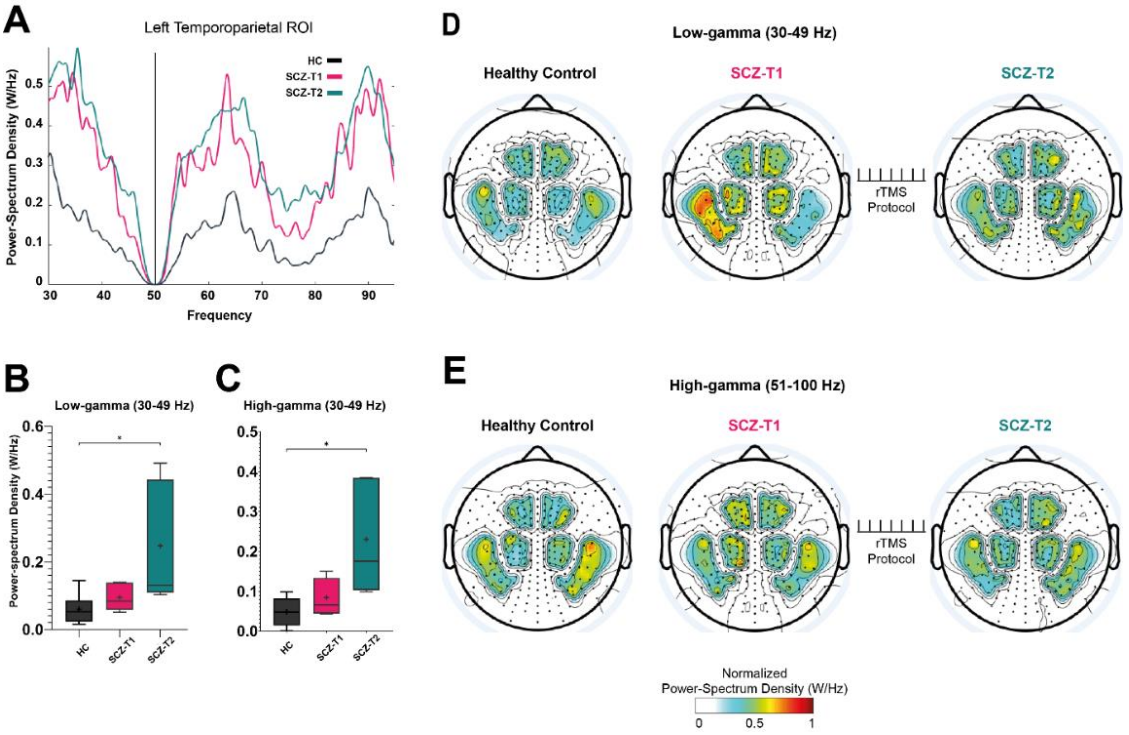


Figure 4-44 Auditory-motor task *performed with the non-dominant hand during DE (NCA). PSD of low and high gamma activity (A, B and C) with "bird-eye" view PSD maps representing cortical distribution of gamma activity in six ROI (D and E).*

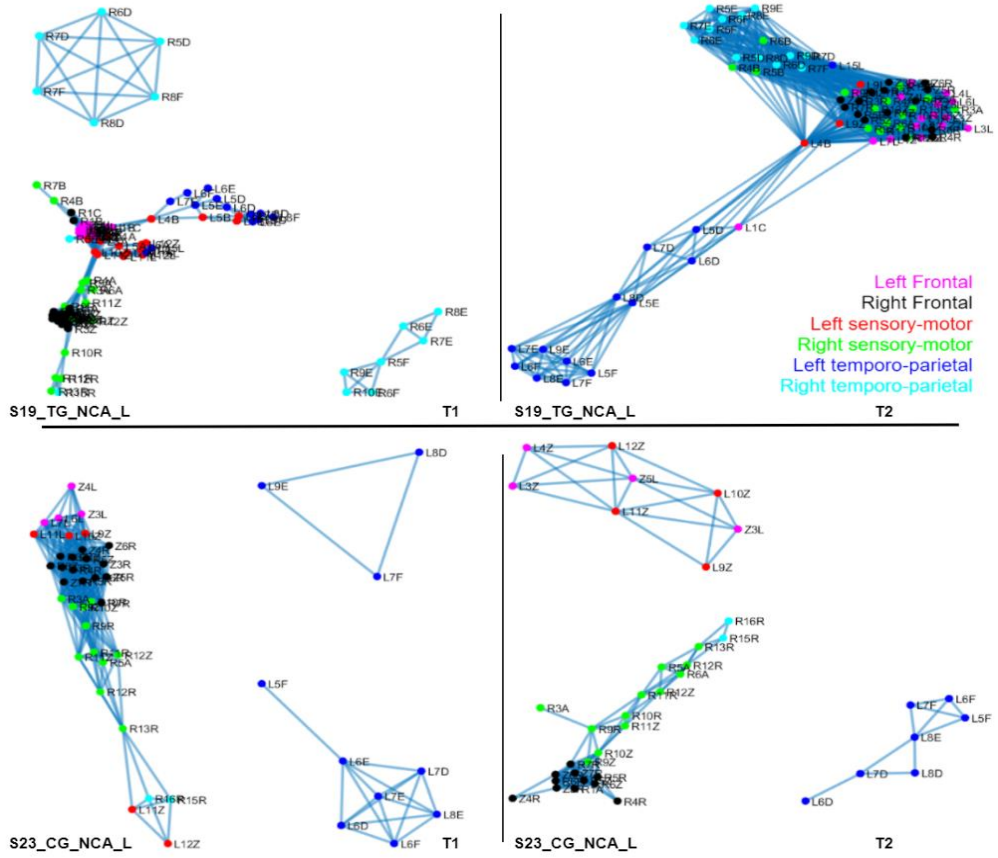


Figure 4-43 *Graph theory in two patients with schizophrenia performing an auditory-motor task before (T1) and after 10 days RTMS (T2). NCA = non-cortical activation. S19 (top) received RTMS at T3-P3, S23 received RTMS at Cz EEG location.*

5 Chapter. Discussion

The aim of the research presented in this thesis dissertation was to analyze the effects of RTMS treatment in patients with schizophrenia and pharmaco-resistant auditory verbal hallucinations by looking at changes in psychometric scores. Exploratory objectives were to investigate a set of neurophysiological markers like ERP, EEG relative power, network connectivity, and inhibitory systems of sensory gating measured with TMS or finger electricity.

Concepts

5.1.1 Sensory gating with P50 and P300 passive task

In ***Study 1***, it was expected that sensory gating measured with P50 sensory potential would improve after RTMS and that P300 wave measured from an auditory oddball paradigm, which is known to be impaired in patients with schizophrenia would increase after the treatment. The work showed that P50 gating is a very difficult measurement when the EEG signal is obtained from high-density EEG. Thus, it would be hazardous to evaluate the effectiveness of RTMS using P50 obtained from 256-channel EEG (Marcu et al., 2020). The work proved that paired-click and oddball auditory paradigms used in our study elicited visible P50 and P300 event-related potentials from seven regions of interest we have proposed. Fifteen electrodes selected from 3 parallel lines were selected for each region (**Figure 5-1**).

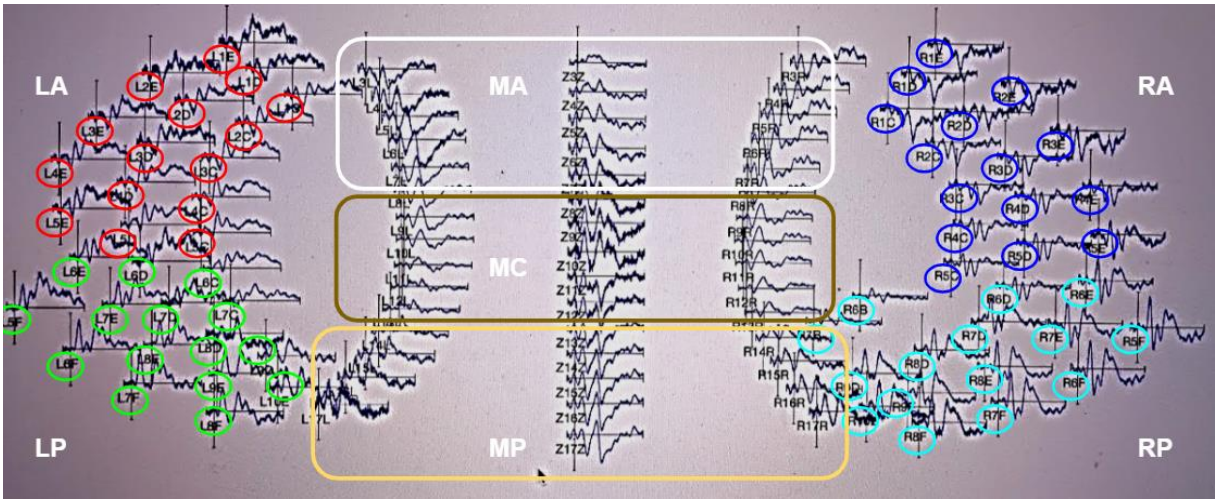


Figure 5-1 *Regions of interest, Study 1 and Study 4. Epochs were set -100 to 900 ms, N1-P3 complex.*

Despite the difficulties we faced with data acquisition and preprocessing, we measured P50 waves (from their peak to the next valley) and we observed that the averaged P50 signal from left temporoparietal and left anterior regions showed major gating in two patients with schizophrenia whereas in two healthy subjects the major P50 gating was observed in mid-central and left temporoparietal regions. Technical aspects of the testing stimulus (S2) and the afferent generated P50 or other MLAEP were criticized because of their latency delay, which appeared later than physiologically expected (**Figure 5-2**). A reason for this might be a temporal gap between the software code initiating the generation of the stimulus and the hardware generating the stimulus (Timm Rosburg, 4th of March 2020, *personal communication*).

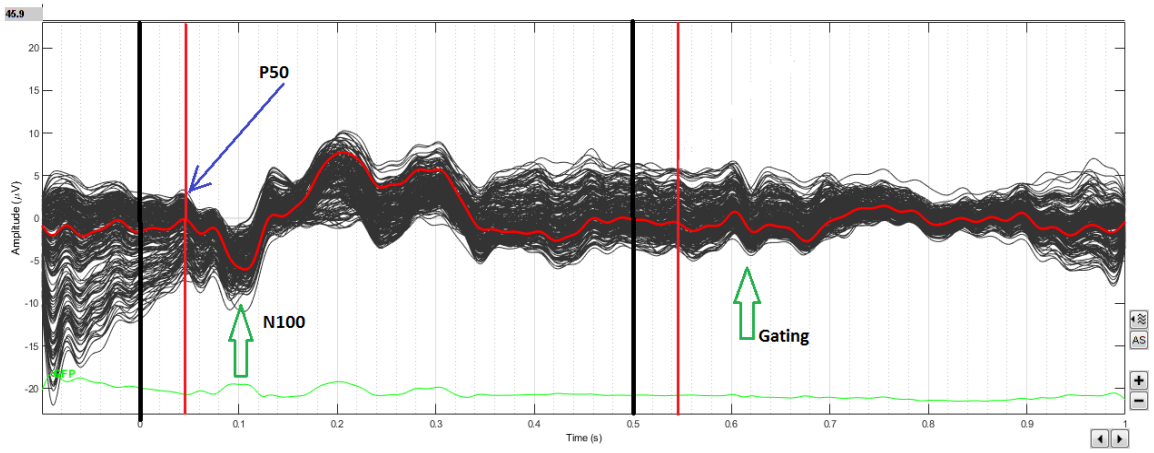


Figure 5-2 *Preprocessing and data inspection of P50 in a HS. Red bars are drawn vertically at 50 ms from 0 and 500 ms. These markers correspond to S1 and S2 auditory stimuli (black bars).*

P300 waves were obtained using the auditory oddball paradigm. For the P300 amplitude, we calculated the maximum voltage between the most negative wave (i.e., N1 component) and the following most positive wave (i.e., P2-for frequent or P3-for deviant components) within the time range of 80-500 ms.

As available in the online literature, a single study used this type of measurement, by calculating a maximum voltage of the N1 and P3 ERP components. This was an Icelandic study aiming to investigate the pharmacodynamic response to nasally administered diazepam. The authors called this type of measure *P300-N100 difference* (Lindhardt et al., 2001). This represents the sum of N1 and P2 components (for the *frequent* stimulus) or N1 and P3 components (for the *rare* stimulus). We named it the ***N100-P300 complex***.

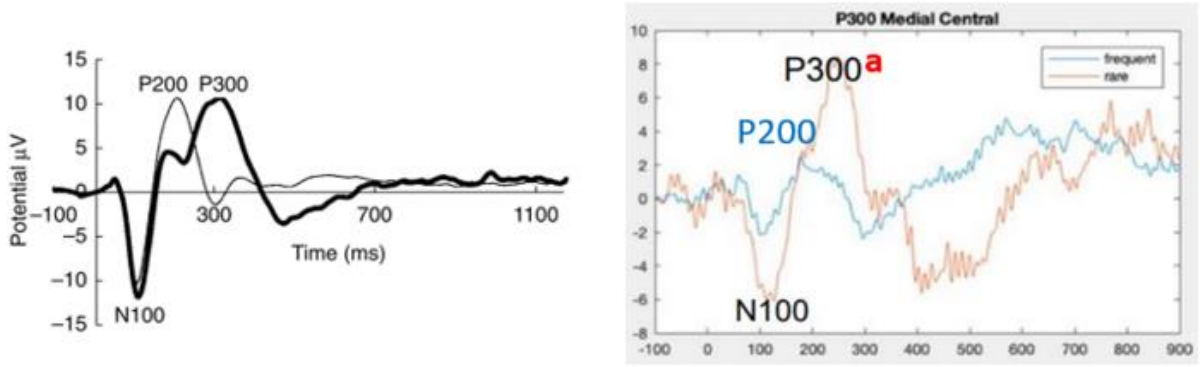


Figure 5-3 ***Active auditory oddball paradigm*** *(Left) and* ***Passive auditory oddball paradigm*** *(Right). ERPs at the vertex electrode elicited by frequent nontarget events (1000 Hz tones, thin line) and rare target events (2000 Hz tones, thick line), respectively. Mean value from seven healthy subjects (Left). Reprinted from British Journal of Clinical Pharmacology, Authors: Lindhardt, K., Gizurarson, S., Stefánsson, S.B., Òlafsson, D.R. and Bechgaard, E. (2001), Electroencephalographic effects and serum concentrations after intranasal and intravenous administration of diazepam to healthy volunteers., 52: 521-527. With permission from John Wiley and Sons, License, Nov 13, 2021 https://doi.org/10.1046/j.0306-5251.2001.01486.x Data from one healthy participant (Right). P300 latency is shorter during the passive task (P300a).*

At baseline, our results showed differences in N100-P300 complex topographical distribution between patients and healthy subjects. HC showed higher amplitudes on the graphs with topographical representation in the left and right anterior regions, mid anterior and mid-central regions, while the patients with schizophrenia showed better representation over left anterior, right anterior, and posterior regions and less amplitude from the midline (Figure 3-7, Figure 3-8, Figure 3-9). These results of P300 reduced amplitude at Cz and Pz electrodes in

patients with schizophrenia compared with healthy subjects followed similar observations like in previous studies (Ford et al., 2001; Stefánsson & Jónsdóttir, 1996).

After 10 sessions of low-frequency 1Hz RTMS, all patients (TG + CG) showed reduced N100-P300 complex voltage at the mid posterior region, with two TG patients showing reduced voltages in all regions (**Figure 3-8**). This was in contradiction with our hypothesis that RTMS will increase P300 amplitude after the treatment.

5.1.2 Habituation of the P300 wave, the passive task

Typically, auditory, or visual oddball paradigms are performed with active or passive subjects' participation. The P300 ERP component is sensitive to the nature of the subject's response during discrimination tasks (Polich, 1987). In the normal "active" oddball paradigm, subjects are asked to count or make some active behavioral response to, the infrequent stimulus. It was suggested that these responses are "controlled" and require voluntary attention. In "passive" oddball experiments the subject is not asked to identify the infrequent stimulus. This passive discrimination task reflects "automatic" processes, using resources of limited capacity (Zurrón & Díaz, 1997). Two distinct late-positive components of the P300 wave were identified. The earlier component, called "P3a" (latency about 240 msec) was elicited by infrequent and unpredictable stimuli whether the subjects ignored the tones. The later component, called "P3b" (latency about 350 msec), occurred only when the subject was actively attending to the tones (Squires et al., 1975).

In our experiments of the auditory oddball paradigm (***Study 1*** and ***Study 5***), we didn´t ask patients to count or to move their fingers when they heard the infrequent stimulus. This method of eliciting P300 was preferred for two reasons: first, to do not affect induced EEG oscillations at parietal regions (i.e., by counting) or sensory-motor areas (i.e., by moving a finger), and secondly, we tried to avoid additional workload or neural effort from the patients, who might have been at different arousal states during the baseline or post-RTMS conditions. By performing the task with a minimum of attentional resources for all patients and healthy subjects we hoped to ensure the uniformity within-subjects and posterior inter-group comparisons.

Habituation can be interpreted as a basal form of neuronal plasticity and can be described as learning that a stimulus becomes without biological significance. A well-known reflex that habituates is the orienting reflex (OR) described by Pavlov (1927) in which the active (voluntary) attention is replaced by passive (involuntary) attention to the novel stimulus (Stekelenburg, 2002). P300 evoked potential obtained from a passive oddball paradigm, in which target stimuli are following the frequent stimuli was found to show habituation processes (i.e., decreased amplitude) in a manner similar to that for OR habituation (Polich, 1989). This habituation process, in which P300 amplitude declines with repeated stimulus presentations is more evident in passive auditory oddball paradigms, but the rate of habituation appears to be much less than phenomena related to the orienting response elicited with auditory or visual stimuli (Bennington & Polich, 1999).

As mentioned before, the hypothesis was that RTMS might modulate the P300 event-related potential by improvements in cognitive function similarly as seen with the antipsychotic quetiapine treatment (Park et al., 2010).

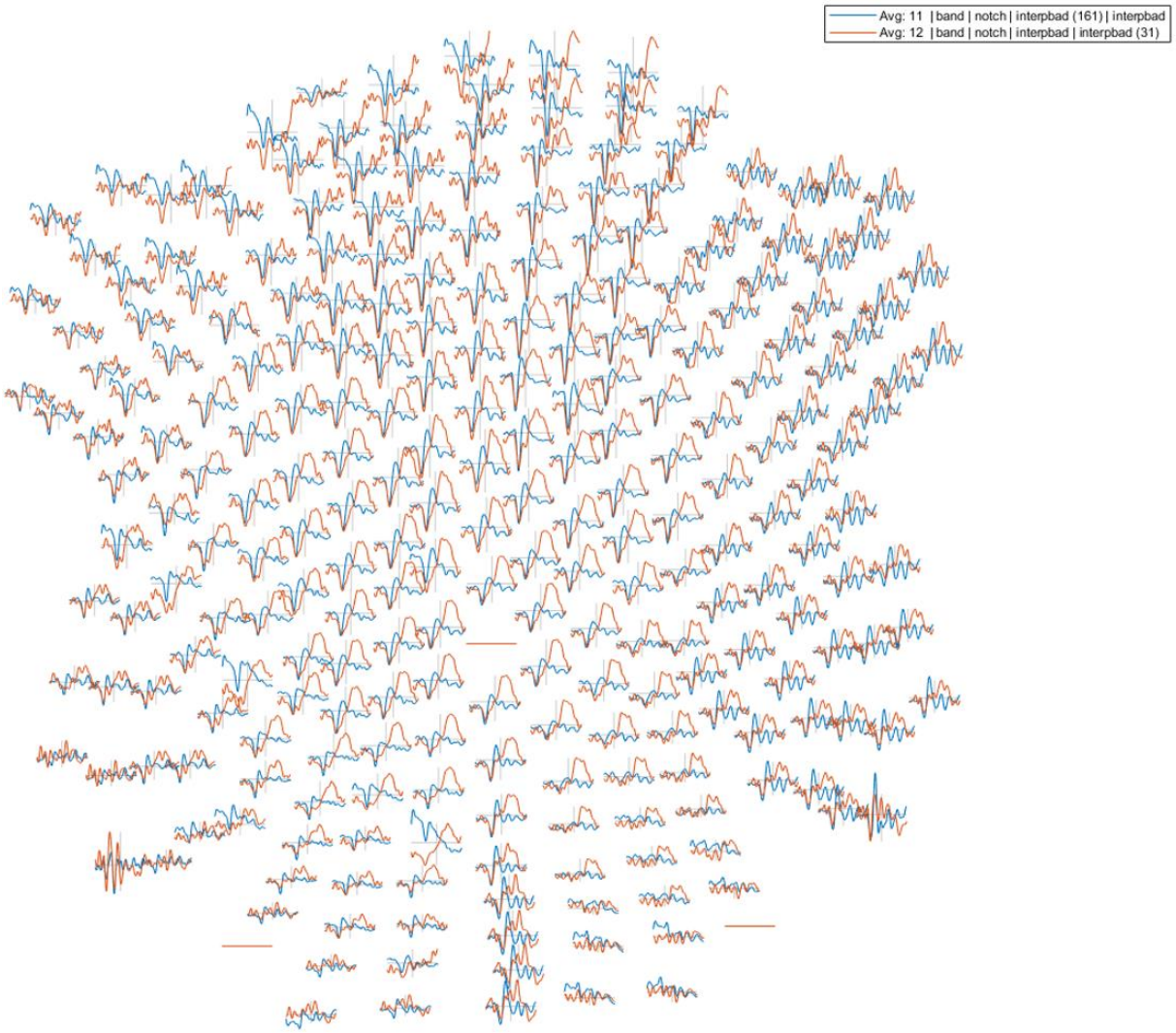


Figure 5-4 *The N100-P200 complex (blue) averaged from 161 frequent stimuli and N100-P300 complex (orange) averaged from 31 deviant stimuli. Passive auditory oddball paradigm in one healthy participant.*

In our study, the N100-P300 complex is formed by N100 and P200 waves (*frequent* stimulus) and by N100 and **P300a** (*infrequent* or *rare* stimulus) (**Figure 5-4**), and the expected amplitude increment did not occur after RTMS treatment. Conversely, the P300 amplitude decreased with RTMS in most of the patients, especially over the mid-central region. If this process is related to a worsening of the patient symptoms or to the technical limits of dense-array 256 channel EEG acquisition and preprocessing remains unclear as it remains unclear that a possible higher habituation rate after the RTMS closer to that observed in healthy controls (Polich, 1989) can be interpreted as a sign of improvement.

Therefore, our data must be carefully interpreted and to avoid any conclusion. Further research and measuring the ***P300a habituation rate*** are necessary for patients with schizophrenia and antipsychotic effective medication (done before and after the treatment), to demonstrate the theory that RTMS modulates in a positive way the habituation automatic properties in patients with schizophrenia.

5.1.3 Silent period elicited with TMS and finger electricity

In the work presented here (***Study 3***) we hypothesized that RTMS treatment might influence CSP and CuSP in patients with schizophrenia and pharmaco-resistant auditory verbal hallucinations by enhancing the total duration.

Cortical silent period duration showed circadian changes increasing from the morning to the evening with up to 15 ms (Lang et al., 2011), and it was prolonged after antipsychotic medication (Daskalakis et al., 2008; S.-K. Liu et al., 2009) or with other drugs like lorazepam, zolpidem, vigabatrin, carbamazepine, gabapentin, and citalopram (Caipa et al., 2018). Our patients were poly-medicated and sometimes they arrived with a diminished arousal state.

CSP and CuSP duration showed variability after RTMS with increased or decreased values in both TG and CG patients. An interesting result we obtained in the S15 subject who was treated at the left temporoparietal region. At baseline (T1), the CSP duration was reduced in comparison with CSP from other younger subjects or healthy participants and it showed similar values within one week after RTMS and after 3 months from the treatment. In change, the CuSP showed increased duration after RTMS which decreased after 3 months (T4).

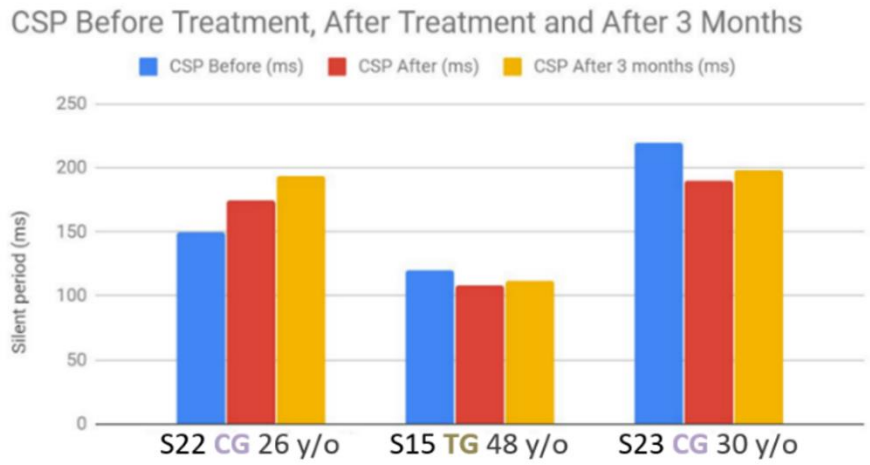


Figure 5-5 *Cortical silent period in patients with schizophrenia before T1 (blue) and after RTMS T2 (red), and T4 (yellow).*

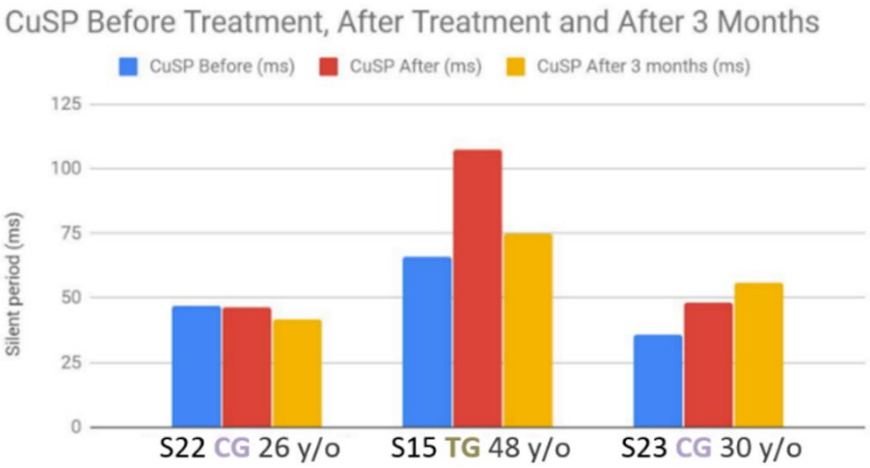


Figure 5-6 *Cutaneous silent period in patients with schizophrenia before T1 (blue) and after RTMS T2 (red), and T4 (yellow).*

5.1.4 N100 and gating of MLAEP

Study 4 was oriented to investigate the sensory gating based on larger components of the mid-latency evoked potentials and data was compared with psychometric scores. We hypothesized that T3-P3 RTMS would improve AVH severity, QoL, and DASS. Additionally, we looked to N100 and P200 evoked potentials with two techniques: "baseline to peak" as previously performed by Nathou et al (Clément Nathou et al., 2018) and "peak to peak" as analyzed in previous studies by Boutros et al and Thoma et al (Nashaat N Boutros et al., 2004; Thoma et al., 2017). We did not find any significant RTMS effects on AVH severity, DASS, or QoL global scores between T3-P3 and Cz RTMS treatments. Regarding neurophysiological data, when compared to HC, TG patients showed the most marked change after T3-P3 RTMS in N100 "peak to peak" measured at mid anterior and mid-central scalp regions which were like the pre-RTMS. No significant effects were seen after RTMS when the coil delivered RTMS at the Cz EEG location. Sensory gating measurements did not show significant changes after RTMS. Thus, all four hypotheses (H1-H4) were false. The study has a small number of participants and therefore it lacks the power to accept the alternative hypotheses.

Despite the encouraging neurophysiological observations seen in patients stimulated over T3-P3 EEG location the results derived from this study are not conclusive to assume that T3-P3 location is superior to Cz EEG location when treating patients with schizophrenia and pharmaco-resistant AVH. Even so, we observed a trend of similar clinical change for both groups with more effects for the T3-P3 RTMS group. There was also a change for the Cz RTMS

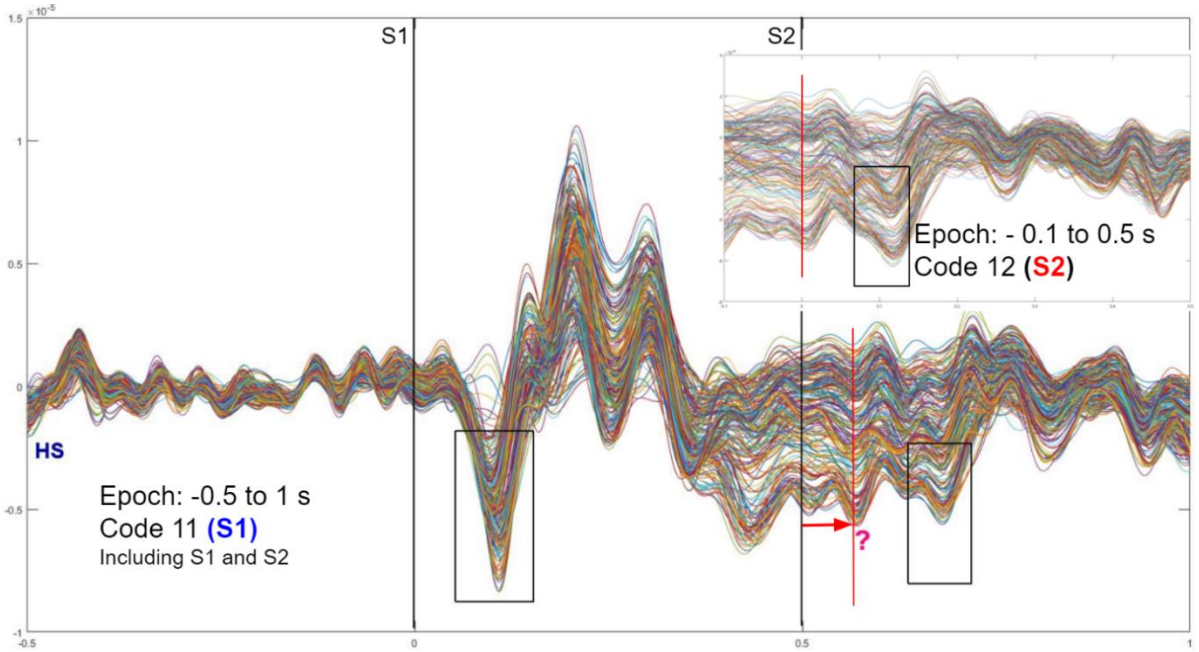


Figure 5-5 *Mid-latency evoked potentials (N100-P200) gating in a healthy subject. The "error of jitter" (red arrow).*

group suggesting that this coil location and active treatment might have induced effects on clinical and neurophysiological outcomes. In fact, vertex stimulation may not always be the ideal control condition as it was observed that short bursts of 1Hz stimulation do lead to widespread changes in neural activity in brain regions associated with the default mode network (Jung et al., 2016). Exploratory and based on the clinical observations we calculated the neurophysiological data for all patients (N=10) (T3-P3 and Cz) in pre-post RTMS conditions and we observed significant changes after RTMS of N100 amplitude to S1 measured "baseline to peak" locally, at left posterior region and central posterior region. The Bonferroni correction adjusted the significance when it was used for one metric (e.g., N1S1Bm) with 7 possible

comparisons (i.e., ROI).

The sample size of our work was small. Thus, we cannot interpret the analysis of a group level, and any certain conclusions should be avoided.

A second inconvenience of this study was the EEG data quality, which can be traced back to the challenge of using a high-density EEG system. During the paired-click paradigm, the sounds S1 (i.e., *conditioning stimulus*) and S2 (i.e., *testing stimulus*) are delivered in a coupled way with an interstimulus interval at 500 ms and an inter-pair interval of 10 seconds to avoid habituation. When the preprocessing was performed with large epochs including both S1 and S2 stimuli, the evoked responses of the second stimulus were seen with a variable delay induced by the software-hardware gap of transmission (T. Rosburg, *pers. comm.*, 2020) (**Figure 5-7**). Thus, N100 latency in epochs of -0.5 to 1 second was not representing the physiological response. To correct this anomaly, the analyses were performed after the EEG epoching of the signal from both S1 and S2 stimuli (from -0.1 to 0.5 second), separately.

The third limitation we faced in this study was the EEG data quality, which can be traced back to the challenge of using a high-density EEG system. This resulted in up to 70% of trial exclusion in each patient group, where 45-75 paired stimuli were analyzed instead of the aimed 150 paired stimuli per participant. ERP recordings with the patients in the supine position, control EEG data online at the time of acquisition, and pretest visualization of the ERP if possible, with routine ERP analysis in 1-2 channels would probably improve the setup of an experiment using 256-channel EEG system.

5.1.5 The multimodal analysis

Study 5 revealed the importance of a multimodal approach while analyzing RTMS treatment effectiveness in patients with schizophrenia and pharmaco-resistant AVH. Two other different neurophysiological measurements were performed to the segments of P300 event-related potentials. These were spectral analyses of event-related oscillations and source-space connectivity.

Here, considering that our auditory oddball paradigm elicited only P300a waves when the infrequent (rare) stimulus was delivered, the P300 described in our paper (Aubonnet et al., 2020) as being related to the frequent stimulus is the P200 wave (N100-P200 complex).

Spectral analyses were assessed with PSD of P300 segments (***Study 5***), during the resting-state or auditory-motor task (***Study 6***).

An index of plasticity was proposed to identify RTMS offline changes. We calculated the difference T2-T1 to observe the change of alpha and beta PSD in case of P300 related oscillations (***Study 5***) or T2/T1 ratio using relative power and PSD when we analyzed EEG activity changes induced by an auditory-motor task (***Study 2*** and ***Study 6***). We represented the change with histogram graphs or "bird-eye" view EEG maps. The relative power of beta activity measured with T2/T1 index showed major changes after RTMS over ipsilateral sensorimotor cortex when the auditory-motor task was performed with the non-dominant hand while gamma activity changes were more sensitive to the dominant hand in all regions.

The PSD increased post-treatment mainly for the alpha band and beta band globally, for six subjects, two in TG and four in CG. No trends were detectable for the gamma and theta bands in the P300 oscillations (***Study 5***). In ***Study 6***, we looked to low gamma and high gamma activity changes during the auditory-motor task, in different epochs: motor cortical activation (MCA) (i.e., 500 ms period after the hand reaction), auditory cortical activation (ACA) (i.e., 500 ms period after the auditory commands), and non-cortical activation (NCA) (i.e., 1 second period in-between the auditory commands). The NCA or "delay epoch" was the only one where the patients with schizophrenia showed higher low- and high-gamma PSD after RTMS .

5.1.6 Network organization and graph theory

Functional specialization and efficient global communication of a brain network are given by the network segregation and integration properties (**Figure 5-8**) which represent crucial information for the brain processing patterns (Rubinov & Sporns, 2010; Sporns, 2003). Specifically, topological segregation (or local clustering) refers to the neuronal processing carried out among groups of regions or within modules while integration refers to the efficiency of global information communication or the ability to integrate distributed information in the network (Cao et al., 2016).

In this work, we used two different metrics of graph-theoretical analyses. In ***Study 5***, the connectivity results using Phase Locking Value (a measure of the phase synchrony between two time-series) showed an increase in ***participation coefficient*** after RTMS for the beta band oscillations evoked by the frequent stimulus of the passive P300 auditory oddball paradigm. This change was seen for seven subjects, four in CG and three in TG, showing that the network became more locally efficient in patients which were stimulated at the left temporoparietal region, but also when they were treated at the vertex (Aubonnet et al., 2020).

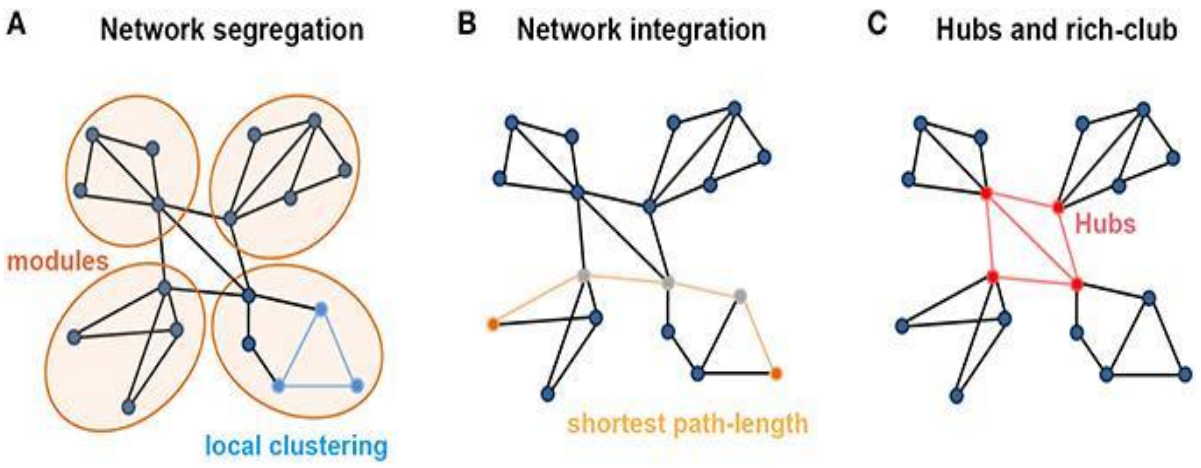
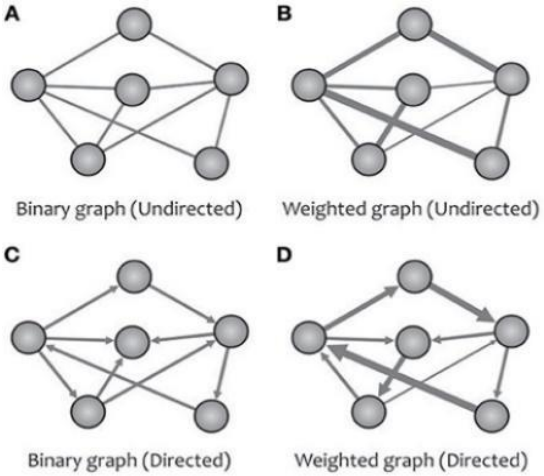


Figure 5-6 *Properties of the brain graph network: (A) Segregation (i.e., connections within modules are much denser than connections between them). (B) Integration (i.e., capacity of the network to communicate between remote regions). (C) High-degree nodes or hubs (i.e., central rich club within the overall network structure). Reprinted with permission granted from Dr. Yong He, Nov 6th, 2021. Copyright © 2016 Cao, M., Huang, H., Peng, Y., Dong, Q., & He, Y. (2016). Toward Developmental Connectomics of the Human Brain. Frontiers in Neuroanatomy, 0, 25.* https://doi.org/10.3389/FNANA.2016.00025

In ***Study 6***, we used the ***small world index*** and ***characteristic path length*** to investigate the phase connectivity derived from Magnitude Squared Coherence (MSC) calculations between each possible pair of ROIs electrodes. Six regions of interest selected at bilateral frontal, sensorimotor and auditory cortices scalp level, (which are supposed to be involved in the auditory-motor anatomical and functional network) provided 102 pairs of cross EEG power spectral density values (17 electrodes/region).

We showed that the small-worldness phenomenon is correlated with the improvement of psychotic symptomatology after the RTMS (SCZ-T2) in a different way than observed before RTMS (SCZ-T1), and we suggested that the small worldness can be a network signature in low-gamma of a possible treatment effect expressed through graph theory and EEG during an AMT performed with the non-dominant hand (Ovidiu C. Banea et al., 2021).



Until now, most brain network studies have focused on undirected graphs (Liao et al., 2017) and functional connectivity. Weighted and directed graph (**Figure 5-9**) analyses would represent the next neurophysiological approach to assess the causal dynamics of neural plasticity with effective connectivity (Z. Liu et al., 2017).

Figure 5-7 *Binary (A, C), weighted (B, D), undirected (A, B) and directed (C, D) graphs. Reprinted with permission granted from Dr. Waldemar Karwowski, Nov 6th, 2021. Copyright © 2019 Farahani, F. V, Karwowski, W., & Lighthall, N. R. (2019). Application of Graph Theory for Identifying Connectivity Patterns in Human Brain Networks: A Systematic Review. In Frontiers in Neuroscience (Vol. 13, p. 585). https://www.frontiersin.org/article/10.3389/fnins.2019.00585*

Statistical analyses

This dissertaion work was structured as a hypothesis-generating study and it laks of sufficient sample size to draw any certain conclusions, based on statistically significant results.

In ***Study 4***, the patient groups were compared to the healthy control group at baseline and the two patient groups were also compared against each other at baseline. Gender comparison was done with a Chi-square test. Outcome measure scores were compared between the two patient groups using ANCOVA when Levene test was non-significant and mixed ANOVA when Levene was significant. If the assumption of sphericity was violated, the Greenhouse-Geisser correction was used. In the end, Bonferroni correction was used to adjust the significance level (i.e., 1 metric in 7 ROI, leading to 7 comparisons). There were no pre-post RTMS differences of clinical symptoms or N100 and P200 waves between TG (patients treated at left temporoparietal region) and CG (patients treated at the vertex). We also performed the analysis for all the patients (N=10) (since we observed similar trends for the clinical outcome in both groups) and one variable, the N100 amplitude measured from baseline to the negative peak showed significant change at the left posterior region with a change from -0.57 μV (SD 0.97) to -2.39 μV (SD 1.59), ($p = 0.006$, $\eta 2 = 0.346$, power 0.83).

In ***Study 5***, the data analysis is descriptive at the group and individual levels. The analysis of the psychometric tests revealed that four out of five subjects in TG and three out of five subjects in CG felt improved condition after the treatment, whereas the other subjects remained neutral or reported worse psychometric scores. In the time domain analysis, the N1-P3 amplitude was globally higher post-treatment than pre-treatment, for six subjects, two in TG and four in CG. The PSD increased post-treatment mainly for the alpha band and beta band globally, for six subjects as well, two in TG and four in CG. The connectivity results showed an increase in participation coefficient during post-treatment for N100-P200 complex, for the beta band especially, for seven subjects, four in CG, three in TG. Due to the small sample size and high variability of the results, we selected study cases and presented them individually (Aubonnet et al., 2020).

Based on the controversial results observed in Study 4 and Study 5, with TG and CG patients showing similar changes on psychometric scores we selected 6 patients from both groups, having the criterion of acceptable EEG data quality, in ***Study 6***. Descriptive statistics were based on median and standard deviation per group and variable. Kruskal-Wallis nonparametric for non-normal data and Two-Way Mixed ANOVA for normal distributed variables tests were performed in each ROI and frequency bands considering three groups (HC, SCZ-T1, and SCZ-T2) as independent variables. Wilcoxon paired tests were applied as post hoc with a corrected p-value for multiple comparisons in those significantly different frequencies and ROIs for PSD analysis. Dunn's post hoc tests were applied within each group in the network analysis. Non-parametric Kendall's tau-b correlation was also applied to describe the relationships between EEG (PSD or connectivity with graphs) variables and psychometric scales before and after the RTMS protocol. Differences were significant if the corrected p-value was < 0.05.

A one-way repeated subject ANOVA showed a significant improvement on psychotic symptoms as measured by PSYRATS between pre - RTMS ($M = 28,6$, $Std = 4,17$) and post - RTMS ($M = 23,6$, $std = 5,27$) conditions, $F(1, 5) = 23,44$, $p < 0,05$, $\eta p^2 = 0,967$. Power spectral density was calculated at the group level (HC, SCZ-T1, and SCZ-T2) during resting state and during a simple auditory-motor task (Nagasawa et al., 2010). The NCA or "delay epoch" was the only one where the patients with schizophrenia showed higher low- and high-gamma PSD after RTMS. Thus, graph theory analysis was used only for this epoch.

Strengths and weaknesses

For this work, we used two active RTMS protocols, at T3-P3 and Cz EEG locations. This approach is very important since the sham conditions of RTMS and placebo effects are considered a major source of bias in the assessment of RTMS efficacy in patients with schizophrenia and AVH (Dollfus et al., 2016). The main strength of the studies presented in this thesis (Study 5 and Study 6) is that they present a multimodal approach with spectral analysis and two different network organization methods with data obtained from a dense-array 256-channel EEG system. By using this technique, we were able to identify functional network properties specific to network segregation and the small worldness effect. Another strength of this work is the use of a simple auditory-motor task which showed major PSD and EEG connectivity differences of low-gamma oscillatory activity during the reference period, in a window located in between the commands, a period related to working memory which is known to be impaired in patients with schizophrenia.

The weaknesses of the works presented here are that they are based on a small sample size. The patients were also undergoing their usual treatment, including antipsychotic and sedative medications. This did not change between pre-and-post RTMS conditions but might have influenced the background neural activity and the generation of the ERPs (Javitt et al., 2008). The experimental procedure was long (1 hour) and tiring and some patients had difficulty cooperating and maintaining tasks engagement, which may have affected data quality. Muscle and movement artifacts added noise to the EEG signal, requiring a thorough pre-processing and the exclusion of many trials.

Summary

This thesis has presented the principles of the diagnosis and the treatment plan for patients with schizophrenia. TMS mechanisms, EEG oscillations, ERP, network organization, cortical and cutaneous silent period, the auditory-motor task, and RTMS are described as methods of neurophysiological investigation.

Study 1 and Study 4 showed that a dense-array 256 channel EEG system is not an easy option to record ERP in patients with schizophrenia when the data is to be analyzed in the time domain. To quantify the RTMS aftereffects in EEG gamma oscillatory activity and network organization, in Study 2 we triggered beta and gamma activity with a cognitively driven auditory-motor task.

Study 3 contains data of the cortical silent period as a measure of central GABAB-mediated cortical inhibition that is linked with sensory gating. The cutaneous silent period which is a peripherally spinal cutaneous-muscular reflex showed similar changes after RTMS in both groups of patients. It remains to complete the work to suggest that this neurophysiological marker is modulated at central CST level or intracortical inhibitory neurons.

Study 5 focused on the relation between psychometric scores and EEG data analysis in time, frequency domains, and functional connectivity. After conducting RTMS, most patients showed an evolution in psychometric data as well as on the neurophysiological quantitative data, independent of the stimulation site. When the psychometric improved post-TMS, we could observe an increased network organization mainly, through the participation coefficient in the beta bands, a higher alpha and beta band power, and different N1-P2 or N1-P3 behavioral responses. In Study 6, we measured the change in phase connectivity and EEG coherence before and after the RTMS by analyzing EEG data obtained from the auditory-motor task with graph theory and small worldness.

Conclusion

This thesis dissertation is a hypothesis-generating research analyzing the influence of RTMS on brain mechanisms in patients with schizophrenia and pharmaco-resistant AVH. Based on the patient´s clinical evaluations and all the neurophysiological measurements it might be suspected that both, left temporoparietal and vertex RTMS induce positive changes in patients with schizophrenia and auditory verbal hallucinations.

By dividing the scalp regions and analyzing ERP data in seven regions of interest we were able to observe local changes of N100 amplitude after the RTMS. This finding suggests that this auditory evoked potential of triggering attention might be an interesting marker of RTMS induced neural plasticity to be analyzed in patients with schizophrenia and AVH.

P300 evoked EEG oscillations spectral analysis did not show group differences before and after RTMS treatment. However, the results suggest that brain connectivity, through the participation coefficient, and PSD, were highly related to the psychometric score and that N1-P3 complex, despite the variability, should be further investigated.

This report revealed for the first time that patients with schizophrenia exhibit higher gamma power spectral density during the auditory-motor task compared to healthy controls, which was modified by RTMS without being significant. PSD of alpha, beta, and gamma oscillatory EEG activity and network organization showed the most marked changes in the prestimulus period or "delay epoch" compared with “auditory” or “motor” windows. The change of low and high gamma PSD was visible, locally, over the left temporoparietal region, when the auditory-motor task was done with the non-dominant hand, showing that during this condition, gamma synchronization can be a marker of “neural effort” and workload during the working memory-related time.

Small worldness index of low gamma activity analyzed in patients with schizophrenia and AVH during the working memory period of an auditory-motor task, when it is performed with the non-dominant hand, showed changes after RTMS similarly to those found in healthy controls. This might represent an interesting biomarker for RTMS treatment effectiveness.

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Appendix

Article I

High density EEG to assess TMS treatment in schizophrenia
Eur J Transl Myol 30 (1): 134-138, 2020

Using high density EEG to assess TMS treatment in patients with schizophrenia

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Abstract

We present preliminary results from the ongoing study entitled "Icelandic AVH-TMS" which aim is to study the effectiveness of repetitive transcranial magnetic stimulation (rTMS) treatment for patients with schizophrenia and with persistent auditory verbal hallucinations (AVH) using symptoms and psychometric scales and high-density EEG system (256 channels). The aim of the present work was to describe cortical topography of the auditory evoked responses like P50 and N100-P300 complex in healthy participants and patients with schizophrenia and to define a robust methodology of signal quantification using dense-array EEG. Preliminary data is shown for three healthy participants and three patients in baseline conditions and for two patients we show the results recorded before and after 10 days rTMS treatment. Our results show differences in sensory gating (P50 suppresion) and a stronger N100-P300 response to rare audio stimulus after the treatment. Moreover we show the value of assessing brain electrical activity from high-density EEG (256 channels) analyzing the results in different regions of interest. However, it is premature and hazardous to assume that rTMS treatment effectiveness in patients with AVH can be assessed using P50 suppression ratio.

Key Words: Transcranial magnetic stimulation, schizophrenia, high density EEG, P50, P300.
Eur J Transl Myol 30 (1): 134-138, 2020

P50 suppression and P300 deficits in patients with schizophrenia were found to be of similar magnitude as findings reported in neuroimaging and neuro-psychology.[1] Dysfunction of sensory gating is of high interest in psychiatric research and has been studied mostly with P50, a positive amplitude wave occurring approximately 50 ms after an auditory stimulus, which likely reflects pre-attentive information processing.[2] Sensory gating deficits using P50 suppression have been found in schizophrenia.[3] P50 gating is not always related to cognitive deficits,[4] and the effect of different treatments on P50 analyzed together with positive or negative symptoms were controversial showing that abnormal sensory gating is not directly associated with the expression of these symptoms.[5] Event related potentials are the most elaborated ERPs in psychiatric studies. The components N100, P200, N200, P300 are elicited by the rare stimuli; whereas frequent stimuli elicit only N100 and P200.[6] During a two-tone discrimination (oddball) task the mean amplitudes of the N100 and P300 auditory responses are decreased in patients with schizophrenia in comparison to the healthy participants.[6,7]

In 1999, Hoffman and colleagues started to explore the repetitive transcranial magnetic stimulation (rTMS) for the treatment of auditory verbal hallucinations (AVH). When the coil was directed at the left temporoparietal cortex, they were able to ameliorate pharmaco - resistant AVH.[8] Since then, many other studies and meta-analyses showed that rTMS is capable of reducing the frequency and severity of auditory hallucinations with significantly better symptom reduction for low-frequency rTMS as compared with placebo.[9-11]. According to the available literature, previous studies describing the effectiveness of rTMS as a treatment for patients with persistent AVH used mainly subjective measurements like psychometric scales. Within the "Icelandic AVH-TMS" study the goal is to assess rTMS treatment with symptoms scales and

neurophysiological markers like ERPs, gamma and beta relative power or cortical silent period.
While the examination of P300 topography in chronically ill patients with schizophrenia and psychotic bipolar disorder was associated with a specific left-lateralized posterior abnormality, suggesting underlying posterior temporal lobe pathology with abnormalities of a generator located in the left superior temporal gyrus (STG),[12,13] the topography of P50 remains largely unknown[14]. Where the P50 suppression and P300 waves show major changes or dysfunction at cortical level remain unclear as most studies reported P300 data at Pz and Cz electrodes while P50 researchers consistently reported analysis at Cz and thus only this location was used for analysis.[1] The objective of this study was to present the method of P50 suppression and N100-P300 components measures from seven different brain locations (left anterior, left posterior, medial anterior, medial central, medial posterior, right anterior and right posterior) using high density EEG. Our hypotheses were that after rTMS treatment, P50 suppression ratio decreases (improved sensory gating) and N100-P300 voltage increases.

Materials and Methods

The patients have been recruited from the psychiatric wards and outpatient clinics through the National Hospital database of diagnosed schizophrenia patients, following the ICD-10 schizophrenia classification (F20). Only those still experiencing persistent auditory verbal hallucinations after finishing at least two 6-8 week drug prescription treatments have been selected. Permission from the Ethics Committee at the University Hospital of Iceland was obtained (approval no. 21.2018). Healthy participants were recruited by convenience sampling and went through Mini-International Neuropsychiatric Interview (M.I.N.I.).

P50 suppression.

The paired-click paradigm was performed to elicit the P50 component. A pure tone (1500 Hz, 6-ms duration at comfortable hearing noise) was used as the click sound and presented during a 500-ms interval through headphones. The interval between paired stimuli was 10 seconds. We presented 150 paired stimulus in 5 blocks with interstimulus interval of 10 seconds, which provided 25 minutes of EEG measurement.[15] In consideration of participant load and ear comfort that could influence EEG measurement, we instructed participants to watch a silent film and presented auditory stimuli from headphones as mentioned above. The S1 response was identified as the most prominent peak in the 40- to 80-ms post stimulus window (Figure 1). The preceding negative trough was used to calculate the S1 amplitude. For the S2 response, the positive peak with latency closest to that of the S1 peak was selected. P50 suppression was calculated as the ratio of the mean value of the S2 amplitude to the mean value of the S1 amplitude (S2:S1).[16,17]

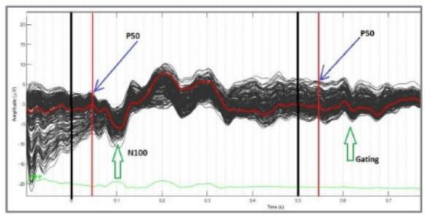

Fig 1. *P50 and N100 gating during preprocessing (black bars correspond to stimulus onset, ISI 500ms).*

N100-P300 complex.

In our study P300 response was measured with an auditory oddball paradigm attention task. The recordings were carried out between 11:00 and 14:00 hours. The subjects were sitting in a comfortable chair with their eyes closed. The frequent (F) and the rare (R) auditory stimuli were presented binaurally through headphones at an interstimulus interval between tones of constant 1.1 sec. For each subject there was 1 trial of 160 tones which occurred randomly with a probability of 0.2.[18] We instructed the participants to pay attention at the rare stimuli without counting or moving a finger.

EEG pre-processing and analysis.

The EEG was recorded using 256 channel system (ANT Neuro, Netherlands) with an electrooculogram (EOG) electrode placed below the right eye, and a ground electrode placed on the left side of the neck. Data pre-processing and analysis was performed with Brainstorm[19] and MATLAB 2018b. The data were sampled at 1024 Hz and re-referenced to the average of left and right mastoid electrodes (R19R, L19L). A bandpass filter was set between 0.1- 80 Hz,[20,21] and notch filter from 49-51 Hz was used to remove undesired monomorphic artifacts from 50 Hz mains electricity.[22] Bad channels were removed when EEG voltage was greater than ±80 μV; if more than 10% of the channels showed to much noise or bad signal, the whole trial was rejected. For P50 analysis the signals were digitized for an epoch of 500 ms starting 100 ms prior to the presentation of each auditory stimulus (-100 ms to +400 ms) and for P300 response analysis the signals were digitized for each epoch of 1000 ms starting 100 ms prior to the presentation of each auditory stimulus (-100 to +900 ms).[20] Baseline correction was performed using pre stimulus 100 ms window and "bad" channels were removed and interpolated. Individual trials were visually inspected and rejected when indicative of excessive muscle activity, eye movements or other artifacts.

The Regions of Interest

The regions of interest (ROI) were defined using a matlab script, each of them being represented by 15 electrodes

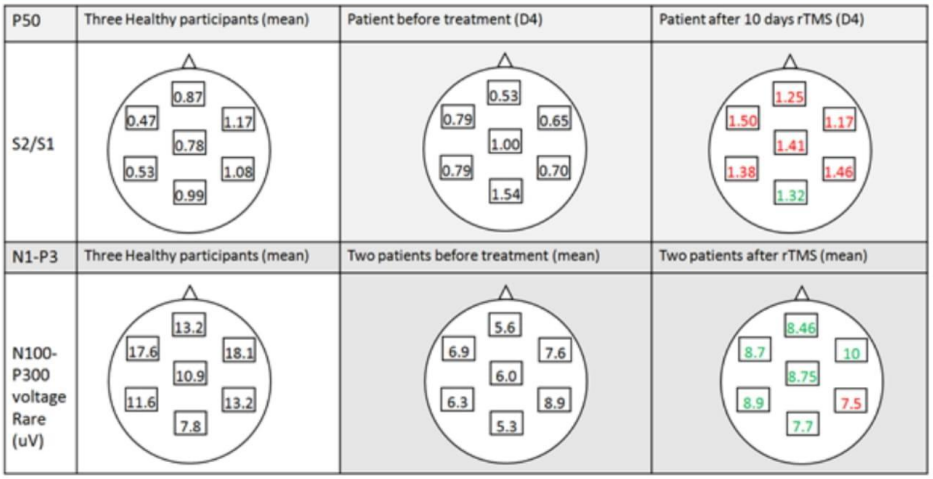

Fig 2. *P50 suppression ratio in three healthy subjects and one patient with schizophrenia before and after rTMS treatment. N100-P300 voltage measurements in three healthy subjects and two patients with schizophrenia. Data was calculated (uV) by averaging 15 channels responses corresponding to 7 ROI: left anterior, left posterior, medial anterior, medial central, medial posterior, right anterior and right posterior.*

(105 electrodes out of 256) as follow: Left Anterior (LA), Left Posterior (LP), Medial Anterior (MA), Medial Central (MC), Medial Posterior (MP), Right Anterior (RA) and Right Posterior (RP). Fifteen electrodes were selected from 3 parallel lines for each region. We measured the peak-to-peak P50 amplitude from a preceding negative trough to the positive peak at 30-70 ms range from the stimulus onset. N100-P300 complex values for each ROI were calculated as the difference between the most negative voltage value and the most positive voltage value within the time range of 80-500 ms. In this work P50 suppression ratio and N1-P3 wave's signals were represented as the average of the fifteen channels of every ROI.

Results and Discussion

Recording event related potentials with high density EEG system is challenging and difficult. Our preliminary data showed major P50 suppression (reduced ratio) in healthy participants than in the patients group (Figures 2 and 3). The patients showed higher ratios on the left anterior and left posterior regions suggesting that these regions might be functionally affected or that the gating in healthy participants is higher on the left anterior and left temporoparietal cortex (Figure 3). N100-P300 components were obtained and visible in the healthy group while patients with schizophrenia showed reduced or absent deviant stimulus responses before the treatment, which changed and was more visible after the

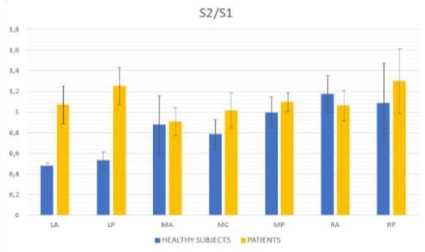

Fig 3. *P50 gating in three healthy participants and three patients with schizophrenia (baseline).*

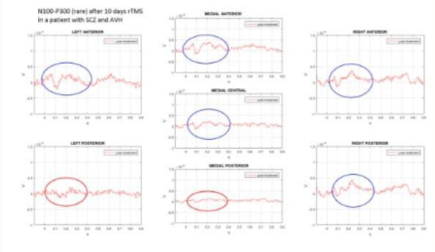

Fig 4. *N100-P300 (rare stimulus) in one patient after 10 days rTMS treatment.*

treatment (Figure 4). Even so, the automatic maximum – minimum voltage measurements for 15 electrodes in each ROI detected higher responses in the patients group in few occasions which at visual inspection resulted to be erroneous due to original signal difficult acquisition or data processing. P50 suppression ratio analyzed in one patient after 10 days rTMS treatment at left temporoparietal region (T3-P3 EEG location) was increased, which is in contradiction to our hypothesis.

The main limitations of the present study are the limited sample size, the lack of a comparator group, the patients' symptoms and medications, which are not presented in this work and the data processing, mostly of P50 waves which are of order of microvolts. It would be of interest to assess N100 gating responses from the same datasets as for P50 due to better visibility and higher amplitude. P300 deviant stimulus absent responses in patients group in baseline condition might be related to the fact that we did not performed classical P300 oddball task with requirement of motor movements or counting of rare stimuli in order to not alter the cortical responses in motor areas or parietal lobes. P300 waves obtained in healthy participants and in two patients after rTMS treatment might be represented by P300a (220–280 ms) related to a novelty or context updating paradigm.

In conclusion, we proved that recording P50 and ERP is possible using HD-EEG 256 channels and the results in healthy subjects are reproducible and show similar topography when studying the different regions of interests. In the patients group we observed that P50 waves are very difficult to measure and the relatively small amplitude or the gated responses cannot be measured with our protocol. A lot of data will have to be excluded from the final analysis. N100-P300 complex is measurable for all selected regions and it appears to be a helpful neurophysiological marker in assessing if ERPs components change after rTMS treatment at the stimulation site or in other different cortical areas.

List of acronyms

AVH – Auditory verbal hallucinations
ERP – Event-related potentials
ROI – Region of interest
rTMS – Repetitive transcranial magnetic stimulation

Authors contributions

S.M., E.P., E.Í., R.A. and O.C.B. processed the experimental data and performed the analysis, S.M., V.D.J., A.D.J., E.Í., E.P., R.A. and O.C.B. performed the measurements, A.D.J, E.Í and O.C.B. performed the 10 days TMS treatments, P.G. O.C.B. and V.D.J. were involved in planning and supervised the work, O.C.B., S.M., E.P. and R.A. drafted the manuscript and designed the figures. All authors discussed the results and commented on the manuscript.

Acknowledgments

The authors wish to thank the University Hospital Landspitali in Reykjavík for infrastructural support.

Funding

None.

Conflict of Interest

The authors declare they have no conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Submitted: February 15, 2020
Revision received: March 4, 2020
Accepted for publication: March 4, 2020

Article II

frontiers in Neuroscience

ORIGINAL RESEARCH
published: 20 November 2020
doi: 10.3389/fnins.2020.575538

P300 Analysis Using High-Density EEG to Decipher Neural Response to rTMS in Patients With Schizophrenia and Auditory Verbal Hallucinations

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Specialty section:
This article was submitted to Brain Imaging Methods, a section of the journal Frontiers in Neuroscience

Received: 23 June 2020
Accepted: 23 October 2020
Published: 20 November 2020

Citation:
Aubonnet R, Banea OC, Sirica R, Wassermann EM, Yassine S, Jacob D, Magnúsdóttir BB, Haraldsson M, Stefansson SB, Jónasson VD, Ívarsson E, Jónasson AD, Hassan M and Gargiulo P (2020) P300 Analysis Using High-Density EEG to Decipher Neural Response to rTMS in Patients With Schizophrenia and Auditory Verbal Hallucinations. Front. Neurosci. 14:575538. doi: 10.3389/fnins.2020.575538

Schizophrenia is a complex disorder about which much is still unknown. Potential treatments, such as transcranial magnetic stimulation (TMS), have not been exploited, in part because of the variability in behavioral response. This can be overcome with the use of response biomarkers. It has been however shown that repetitive transcranial magnetic stimulation (rTMS) can the relieve positive and negative symptoms of schizophrenia, particularly auditory verbal hallucinations (AVH). This exploratory work aims to establish a quantitative methodological tool, based on high-density electroencephalogram (HD-EEG) data analysis, to assess the effect of rTMS on patients with schizophrenia and AVH. Ten schizophrenia patients with drug-resistant AVH were divided into two groups: the treatment group (TG) received 1 Hz rTMS treatment during 10 daily sessions (900 pulses/session) over the left T3-P3 International 10-20 location. The control group (CG) received rTMS treatment over the Cz (vertex) EEG location. We used the P300 oddball auditory paradigm, known for its reduced amplitude in schizophrenia with AVH, and recorded high-density electroencephalography (HD-EEG, 256 channels), twice for each patient: pre-rTMS and 1 week post-rTMS treatment. The use of HD-EEG enabled the analysis of the data in the time domain, but also in the frequency and source-space connectivity domains. The HD-EEG data were linked with the clinical outcome derived from the auditory hallucinations subscale (AHS) of the Psychotic Symptom Rating Scale (PSYRATS), the Quality of Life Scale (QoLS), and the Depression, Anxiety and Stress Scale (DASS). The general results show a variability between subjects, independent of the group they belong to. The time domain showed a higher N1-P3 amplitude post-rTMS, the frequency domain a higher power spectral density (PSD) in the alpha and beta bands, and the connectivity analysis revealed a higher brain network integration (quantified using the participation coefficient) in the beta band. Despite the small number of subjects and

the high variability of the results, this work shows a robust data analysis and an interplay between morphology, spectral, and connectivity data. The identification of a trend post-rTMS for each domain in our results is a first step toward the definition of quantitative neurophysiological parameters to assess rTMS treatment.

Keywords: high-density EEG, TMS (repetitive transcranial magnetic stimulation), P300, schizophrenia, spectral analysis, temporal analysis, brain connectivity

1. INTRODUCTION

Hallucinations are sensory perceptions occurring in the absence of an external stimulus. Auditory verbal hallucinations (AVH) are positive psychotic symptoms of schizophrenia and a diagnostic feature in the pathology, occurring in an estimated 60–70% of people with this disorder. An increased interaction among the auditory-language and striatal brain regions occurs while patients hallucinate (Ćurčić Blake et al., 2017). Patients with AVH present evidence of structural brain alterations associated with these perceptions, such as reduced gray matter volume in the superior temporal gyrus (Kasai et al., 2003), including the primary auditory cortex, and abnormal connectivity among the temporal, prefrontal, and anterior cingulate regions (Homan, 2013; Ćurčić Blake et al., 2017). Among the empirically supported theories of the origin of AVH, are a misinterpretation of inner speech (Frith and Done, 1988) and aberrant activation of the auditory cortex (Dierks et al., 1999). Almost one-third of patients with positive psychotic schizophrenia present treatment resistant symptoms (Howes et al., 2009) and there is a compelling need for novel treatments.

Transcranial magnetic stimulation (TMS) is a non-invasive method used over the past 25 years in the treatment of neurobehavioral disorders (Stanford et al., 2008). It uses an alternating magnetic field to induce an electrical current in the brain, depolarizing neurons and generating action potentials. Wassermann et al. (1996) and Chen et al. (1997) reported that 1 Hz repetitive TMS (rTMS) reduces the excitability of cortical neurons in healthy individuals. Based on these effects, Hoffman et al. (1999) hypothesized that 1 Hz rTMS delivered to the left temporoparietal cortex reduced activity in receptive language areas associated with AVH in patients with schizophrenia. Neuroimaging studies of AVH showed an increased activation in the absence of an external stimulus in the left primary auditory cortex of subjects with this symptom (Kompus et al., 2011).

Our goal was to establish a methodological tool to quantitatively assess the cognitive processes of people suffering with AVH. We aimed to develop an hypothesis that can validate psychometric results with event related potential (ERP) morphology (time domain), power spectral density (frequency domain), and brain connectivity in patients undergoing 10 sessions of low-frequency rTMS.

To date, the mechanism of the effect of rTMS on AVH has only been inferred from the hypothesis of left temporoparietal cortex dysfunction and the behavioral response is variable from patient to patient. Dozens of studies have used inhibitory low frequency rTMS over the T3-P3 EEG location as a treatment for pharmaco-resistant AVH with the effects measured mainly with psychometric scales (Lefaucheur et al., 2014; Slotema et al., 2014). Physiological measures linked to specific brain areas and biomarkers of target engagement and response are needed to optimize treatment. Indeed, response biomarkers are essential as predictors of treatment where behavioral outcomes can be variable. They may also be very useful for rTMS treatments, where multiple parameters, including frequency, train length, intensity, duration, and treatment schedule can all influence effectiveness and should be optimized before full-scale clinical trials are attempted. Past studies indicate a relation between different frequency bands and cognitive processes (Klimesch et al., 1998). The power spectral density (PSD) changes observed in response to attentional demands can be of interest to monitor patients with schizophrenia behavior. Electroencephalographic (EEG) measures, including spectral density and evoked potentials (Barr et al., 2011), have been used as measures of the physiological response to TMS treatment. For instance, it has been observed that rTMS to the dorsolateral prefrontal area increased the P300 response in patients with schizophrenia, but not healthy controls (Lin et al., 2018).

The P300 first described by Sutton et al. (1965), mostly studied as a parameter of voluntary attention (Mazaheri and Picton, 2005), is the leading Event Related Potential (ERP) correlate of target discrimination (Mazaheri and Picton, 2005) and it has been largely employed to characterize schizophrenia (Jeon and Polich, 2003). Previous studies have found that patients with auditory hallucinations exhibit reduced P300 amplitudes (Jeon and Polich, 2003; Bramon et al., 2004; Fisher et al., 2014). Many works based on P300 also analyzed N100, the negative deflection that occurs approximately 100 ms after the auditory stimulus, noting a relation with working memory (Lijffijt et al., 2009). The mean amplitudes of the auditory N100 and P300 responses are decreased in patients with schizophrenia in comparison to healthy participants (Ogura et al., 1991; Ford et al., 2001; Earls et al., 2016).

Here, we compared alterations in the P300 response after left temporal and vertex [used as a control in previous studies with schizophrenia and AVH (Nyffeler et al., 2006; Nowak et al., 2008; Loo et al., 2010)] TMS in patients with schizophrenia using three different approaches : time, frequency,

Abbreviations: AHS, Auditory Hallucinations Subscale; AVH, Auditory Verbal Hallucinations; CG, Control Group; DASS, Depression Anxiety Stress Scale; ERP, Event-related Potential; HD EEG, High Density Electroencephalogram; PC, Participation coefficient; PSD, Power Spectral Density; PSYRATS, Psychotic Symptom Rating Scales; QoLS, Quality of Life Scale; rTMS, Repetitive Transcranial Magnetic Stimulation; TG, Treatment Group; TMS, Transcranial Magnetic Stimulation.

and source-space connectivity. Patients also underwent a battery of neurobehavioral and tests before and after treatment.
We remained descriptive in our analysis before and after treatment, at group and single levels.

2. MATERIALS AND METHODS

2.1. Participants

The patients were recruited from the psychiatric wards and outpatient clinics of the National Hospital of Iceland. They were diagnosed with schizophrenia, following the ICD-10 (International Classification of Diseases, Tenth Revision, Clinical Modification) schizophrenia classification (F20). Only those still experiencing persistent AVH after finishing at least two 6–8 week drug treatments were selected. Patients were excluded if they had history of seizures, were using cannabis or drinking more than three units of alcohol daily, were using any other illegal drugs within 1 month prior to the beginning of the study, or showing TMS contraindications during the pre-treatment interview (Rossi et al., 2011). Permission from the Health Research Ethics Committee at the University Hospital of Iceland was obtained (approval no. 21.2018). Ten patients (7 men and 3 women, mean age = 32, SD = 6.41) were selected for the study. All of them were taking medications. **Table 1** sums up the patient information. The patients were randomly assigned into two groups. Five patients (four men and one woman, mean age 35.2, SD = 5.12,range 30–48) were included in the active treatment group (TG). They received ten daily sessions of 15 min 1 Hz frequency rTMS (900 pulses/session) at 100% of abductor pollicis brevis resting motor threshold (RMT) applied at T3-P3 location. Five patients (three men and two women, mean age 29.6, SD = 3.92, range 26–39) were included in the control group (CG) and received rTMS at 100% RMT to the vertex of CG 10-20 location. The EEG and psychometric data were acquired twice in each patient group; before the rTMS treatment (pre-treatment) and within 1 week after completing ten sessions of rTMS treatment (post-treatment). This produced 20 datasets: five pre-TMS TG, five post-TMS TG, five pre-TMS CG, and five post-TMS CG. **Figure 1** shows the experimental set-up and workflow designed for this study. **Figure 2** shows the pre-processing and data analysis pipeline used for this study.

2.2. Psychometric Data

Three scales were used to collect clinical information pre- and post-treatment.

2.2.1. PSYRATS

Psychotic Symptom Rating Scales (PSYRATS) auditory hallucinations subscale (AHS) is an interview measuring auditory hallucinations using 11 items rated on a five-point ordinal scale (0–4). The scale measures the severity of AVH for the past week in 11 dimensions which are: frequency, duration, location, loudness, beliefs about origin, negative content, intensity of negative content, amount of distress, intensity of distress, disruption of life, and control. PSYRATS has shown excellent inter-rater reliability and good discriminant and convergent validity for both chronic and first episode psychosis (Haddock et al., 1999; Drake et al., 2007).

2.2.2. Quality of Life Scale (QoLS)

Quality of life was assessed with a 16 item self-report scale, consisting of five conceptual domains of quality of life: material and physical well-being, relationships with other people, social community and civic activities, personal development and fulfillment, and recreation. The scale has been shown to have good test-retest reliability and good convergent and discriminant validity (Flanagan, 1978).

2.2.3. Depression Anxiety Stress Scales (DASS)

The DASS is a measure of mental health focusing on the three traits of depression, anxiety, and stress. It consists of 42 items, rated on a four point Likert type scale of how much that symptom occurred in the last week. In clinical samples the scale has shown excellent internal consistency and temporal stability as well as excellent discriminant validity and good convergent validity (Brown et al., 1997).

2.3. P300 Recordings

P300 was measured with an auditory oddball paradigm attention task. The recordings took place between 11h00 and 14h00 for a duration of 1 h. The subjects sat with their eyes closed. The frequent (F) and the rare (R) auditory stimuli were presented binaurally through headphones at an interstimulus interval between tones of constant 1.1 s. The loudness was adjusted for each participant. For each subject, there was one trial of 200 tones, comporting a random tone occurrence with a probability of 0.2, leading to 160 frequent tones and 40 rare (Marcu et al., 2020). We required the participants to focus on the rare stimuli without counting or moving a finger.

2.4. EEG Pre-processing and Analysis

The EEG was recorded using a 256 channel system (ANT Neuro, Netherlands) with an electrooculogram (EOG) electrode placed below the right eye and a ground electrode placed on the left side of the neck. Data pre-processing and analysis were performed with Brainstorm (Tadel et al., 2011) and MATLAB 2018b (MathWorks, Inc., Natick, 158 Massachusetts, USA).

2.4.1. Pre-processing

The data were sampled at 1,024 Hz and re-referenced to the average of left and right mastoid electrodes (R19R, L19L). A bandpass filter was set between 0.5 and 70 Hz and notch filter from 49 to 51 Hz was used to remove undesired monomorphic artifacts from 50 Hz mains electricity. Bad channels were manually removed when EEG voltage was higher than ± 80 μV; if more than 10% of the channels showed too much noise or incorrect signal, the whole trial was rejected. The signals were digitized in epochs of 1,200 ms, starting 500 ms before the presentation of each auditory stimulus (−500 to +700 ms). Baseline correction was performed using pre-stimulus 500 ms to pre-stimulus 100 ms window and channels marked as bad were removed and interpolated. Individual trials were visually inspected and rejected when indicative of excessive muscle activity, eye movements, or other artifacts.

TABLE 1 | Socio-demographic information.

Group	Id	Gender	Medication	Diagnosis
TG	T1	M	Clozapine, Fluoxetine, Bupropion	Paranoid Schizophrenia
TG	T2	M	Clozapine, Olanzapine, Perphenazine, Alprazolam, Levomepromazine, Oxazepam and Melatonin	Paranoid Schizophrenia
TG	T3	F	Sertraline, Quetiapine, Pregabalin and Zopiclone	Schizoaffective Disorder Depressive type
TG	T4	M	Clozapine and Flupenthixol	Paranoid Schizophrenia
TG	T5	M	Clozapine, Amisulpiride, Propranolol and Clonazepam	Paranoid Schizophrenia
CG	C1	M	Paliperidone, Quetiapine and Perphenazine	Paranoid Schizophrenia
CG	C2	F	Clozapine, Flupenthixol, Zopiclone, Mirtazapine, Escitalopram, Metoprolol and Chlorpromazine	Paranoid Schizophrenia
CG	C3	F	Aripiprazole, Olanzapine, Chlorprothixene and Pregabalin	Paranoid Schizophrenia
CG	C4	M	Clozapine, Olanzapine, Bupropion and Propranolol	Paranoid Schizophrenia
CG	C5	M	Clozapine, Pregabalin, Amisulpride	Hebephrenic Schizophrenia

(Group : TG, T3-P3 group; CG, Cz group. Gender : M, man; F, woman.).

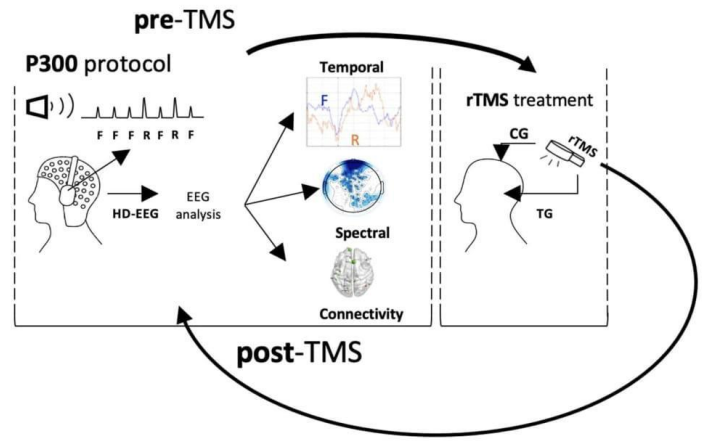

FIGURE 1 | Data acquisition and processing workflow.

2.4.2. Data Analysis

2.4.2.1. Time Domain

N100-P300 complex values of both frequent and rare stimuli were calculated and plotted via MATLAB 2018b for each subject (pre- and post-treatment for patients groups).

The scalp was divided into 5 regions of interest (ROI), see **Figure 2**. The 254 electrodes were partitioned as follows: 80 channels for the Frontal region (F), 59 for the Parietal region (P), 69 for the Occipital region (O), 23 for Right Temporal lobe (RT), and 23 for Left Temporal lobe (LT) (Schartner et al., 2015).

N1-P3 wave signals were calculated for the entire N100-P300 complex from the average of channels of every ROI as the difference between the most negative voltage value within time range of 80–150 ms (N100) and the most positive voltage value within time range of 250–500 ms (P300).

The differences between frequent and rare stimulus and pre- and post-treatment were also computed and plotted.

2.4.2.2. Frequency Domain

The power spectral density (PSD) was computed for each epoch with Welch's method, using Brainstorm, with the following frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), gamma (30–70 Hz). The PSD has been divided by the associated bandwidth for each frequency band.

Using the same scalp division as that of the time analysis, the PSD of electrodes within the same ROI were averaged for frequent and rare stimuli, pre- and post-treatment for each subject.

The PSD difference post-pre treatment and frequent—rare were computed for each subject.

2.4.2.3. Connectivity

The connectivity has been computed at the cortical level using the "EEG source connectivity" method. It consists of estimating the brain sources (over 68 regions of interest—ROI—) and then

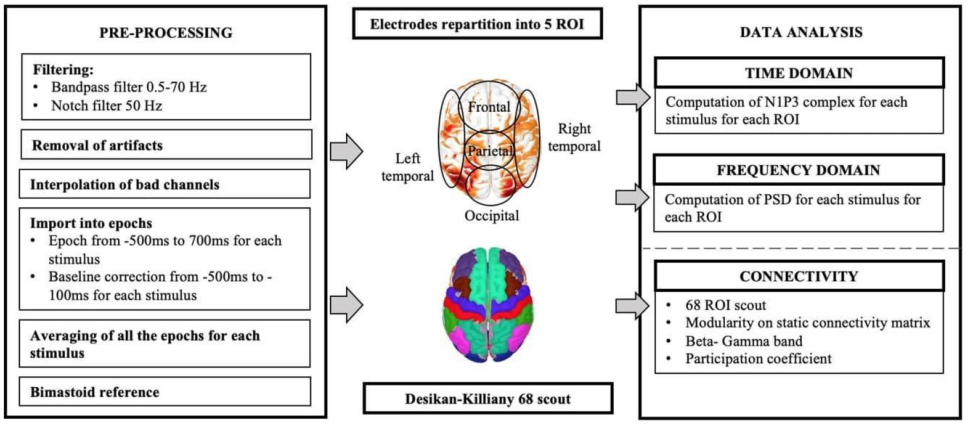

FIGURE 2 | Pre-processing and analysis workflow.

computing the statistical coupling between these reconstructed sources. The weighted minimum norm estimate (wMNE) and the Phase Locking Value (PLV) were used to solve the inverse problem and compute the functional connectivity, respectively. This choice was based on previous comparative studies showing good performance of this combination on simulated and real data. (Hassan et al., 2014, 2017; Hassan and Wendling, 2018). The analysis has been performed only on the beta and gamma bands, due to window length constraints (here 700 ms). The source-space networks were estimated for each trial, subject and conditions. To compare between conditions, the networks were quantified using network measures that allow the extraction of the topological properties of the networks. We made the choice here to focus on network integration as it is the most consistent network feature that changes due to electric/magnetic stimulation (Modolo et al., 2020) or brain disorders (Stam, 2014). The network integration reflects the ability of the brain network to integrate information form different and distant brain regions, a key feature of efficient information processing. To quantify the network integration, we used the participation coefficient (PC), to calculate the interactions between brain modules (distant sub-networks), on the thresholded connectivity matrices (here 20%). We used the brain connectivity toolbox (BCT) (Rubinov and Sporns, 2010) to compute the PC (http://www.brain-connectivity-toolbox.net/).

3. RESULTS

3.1. Group Results

The analysis for each individual revealed general consistent results. The results picturing the evolution (increase or decrease) of the neurophysiological and psychometric data and are detailed in **Table 2** for the TG, and in **Table 3** for the CG. The associated numerical values are detailed in **Table 4** for the TG and in **Table 5** for the CG. The analysis of the psychometric tests revealed that four out of five subjects in TG (**Tables 2**, **4**) and three out of five subjects in CG (**Tables 3**, **5**) felt improved condition after the treatment, whereas the other subjects remained neutral or reported worse psychometric scores. In the time domain analysis, the N1-P3 amplitude was globally higher post-treatment than pre-treatment, for six subjects, two in TG (**Tables 2**, **4**) and four in CG (**Tables 3**, **5**). The PSD increased post-treatment mainly for the alpha band and beta band globally, for six subjects as well, two in TG (**Tables 2**, **4**) and four in CG (**Tables 3**, **5**). No trends were detectable for the gamma and theta bands. In several subjects, the right temporal area showed an opposite behavior compared to the other regions. The connectivity results showed an increased network integration (increase in participation coefficient) during post-treatment for frequent, for the beta band especially, for seven subjects, four in CG (**Tables 3**, **5**), three in TG (**Tables 2**, **4**). Due to the small sample size and high variability of the results, we will discuss selected study cases individually. The following four patients were selected due to their interplay between psychometric score and neurophysiological results, independant of treatment. Two subjects (T2, in TG and C3, in CG) presented an improvement in the psychometric score post-TMS, and the two others presented a stagnation in the psychometric (C2, in CG) or a decrement (T5, in TG). The rest of the data are provided in the **Supplementary Material**. There were no significant changes on AVH severity measured with PSYRATS AHS, in QoL and DASS global scores after rTMS between TG and CG.

3.2. Study Case 1 : Improvement in Psychometric Score

The two patients detailed in this section presented an improvement in their psychometric score post-treatment. We

TABLE 2 | Treated Group: Increase (↑), decrease (↓), or constancy (–) of the value after treatment of N1-P3, Connectivity, Psychometric and Power spectral density (PSD) of the frequent (blue) and rare (orange) stimuli (F, frontal; P, parietal; O, occipital; LT, left temporal; RT, right temporal).

	N1-P3 amplitude (μV)					Connectivity	Psychometrics		
	F	P	O	LT	RT	Participation coefficient (%)	QoL	DASS	PSYRATS
T1	↑↑	-↓	↑↓	↓↓	↑↓	↑	↑	-	↓
T2	↓↓	-↑	↓↓	↓↑	↓↓	↑	↑	↓	↓
T3	-↑	↑↑	↓↓	↓-	–	-	↑	↓	↓
T4	↑↑	↑↑	↑↑	↑↑	↑↑	-	-	-	↓
T5	↓↓	↓-	↓↓	↓↓	↓↓	↑	-	↑	↑

	Power spectral density																			
	PSD: THETA					PSD: ALPHA					PSD: BETA					PSD: GAMMA				
	F	P	O	LT	RT	F	P	O	LT	RT	F	P	O	LT	RT	F	P	O	LT	RT
T1	-↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓-	↓↓	↓↓	↓↓	↑-	↑↑	-↓	↓↓	↑↑
T2	↓↓	↓↓	↓-	↓↓	↓↑	↑↑	-↑	↑↑	↑↑	↑↑	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓
T3	↓↓	↓↓	↓↓	↓↓	↓↑	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↑↑	↑↑	↑↑	↑↑	↑↑
T4	↓↓	↓↓	-↓	↑-	↓↓	↑↑	↑↑	↑↑	↑↑	↓↓	↑↑	↑↑	↑↑	↑↑	↓↓	↑↑	↑↑	↑↑	↑↑	↑↑
T5	↑↑	↑↑	↑↑	↑↑	↓-	↑↑	↑↑	↑↑	–	↓↓	↑↑	↑↑	↑↑	↑↑	↓↑	↑↑	↑↑	↑↑	↑↑	↓↓

QoLS, Quality of Life Scale; DASS, Depression Anxiety Stress Scale; PSYRATS, Psychotic Symptom Rating Scales.

TABLE 3 | Control Group: Increase (↑), decrease (↓) or constancy (-) of the value after treatment of N1-P3, Connectivity, Psychometric and Power Spectral Density (PSD) of the frequent (blue) and rare (orange) stimuli(F, frontal; P, parietal; O, occipital; LT, left temporal; RT, right temporal).

	N1-P3 amplitude (μV)					Connectivity	Psychometrics		
	F	P	O	LT	RT	Participation coefficient (%)	QoL	DASS	PSYRATS
C1	↓↑	↓↑	↓ ↑	↓↑	↓↑	-	-	↓	-
C2	–	↓↓	-↑	↑↑	↑↑	↑	-	-	-
C3	↑↑	↑↑	↑↑	↑↓	↑↓	↑	↑	↓	-
C4	↓↓	↓↓	↓↓	↓↓	↓↓	↑	↓	↓	-
C5	↓↓	↓↓	↓↑	↓↑	↓↑	↑	↓	↑	-

	Power spectral density																			
	PSD: THETA					PSD: ALPHA					PSD: BETA					PSD: GAMMA				
	F	P	O	LT	RT	F	P	O	LT	RT	F	P	O	LT	RT	F	P	O	LT	RT
C1	-↑	↓↓	↓↓	↓↓	↓↑	↓↓	↓↓	↓↓	↓↓	↑↑	↑↑	↑↑	↑↑	-↑	↑↑	↑↑	↑↑	↓-	↓↓	↓↓
C2	↑↑	↑↑	↑↑	↑↑	↑↑	↓↑	-↑	-↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	-↑	↓↓	↓↓	↓↓	↓↓	↓↓
C3	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↓↓	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑
C4	↓↓	↓↓	↓↓	↓↑	↓↓	↓-	–	-↑	↑↑	–	↓↓	↓↓	↓↓	↑↑	-↓	↓↓	↓-	↓↓	↓↑	↓↓
C5	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓

QoLS, Quality of Life Scale; DASS, Depression Anxiety Stress Scale; PSYRATS, Psychotic Symptom Rating Scales.

chose to describe them in this section due to their higher values post treatment in the neurophysiological data, (**Figures 3A**, **4A**) in order to find a potential correlation between those two outcomes.

3.2.1. Patient T2

Patient T2 (**Figure 3**) is a man with paranoid schizophrenia, in the TG, who took part in the study while taking : clozapine, olanzapine, perphenazine, alprazolam, levomepromazine, oxazepam, and melatonin. The psychometric tests (**Figure 3A**) show an improvement of the quality of life post-treatment, a decreased DASS after TMS and decreased PSYRATS post-treatment. The temporal analysis (**Figure 3D**) showed a lower N1-P3 amplitude post-treatment, except for the parietal and left temporal parts. The PSD (**Figure 3B**) showed higher alpha power post-TMS. However, the beta power is lower post-TMS. The

TABLE 4 | Treatment Group: Values pre and post treatment of N1-P3, Connectivity, Psychometric and Power spectral density of the frequent (blue) and rare (orange) stimuli(F, frontal; P, parietal; O, occipital; LT, left temporal; RT, right temporal).

	Connectivity				Psychometrics							
	Participation coefficient (%)				QoL				DASS			
	Pre		Post		Pre		Post		Pre		Post	
T1	1		9		68		77		8		9	
T2	6		13		55		75		92		85	
T3	10		8		50		69		118		53	
T4	9		10		94		91		5		4	
T5	15		26		93		96		39		58	

	Freq				P				O				LT				RT			
	Pre		Post		Pre		Post		Pre		Post		Pre		Post		Pre		Post	
	Freq	Rare	Freq	Rare	Freq	Rare	Freq	Rare	Freq	Rare	Freq	Rare	Freq	Rare	F	Rare	F	Rare	F	Rare
	N1-P3 amplitude (uV)																			
T1	3.52	6.91	4.12	7.33	5.05	10.08	4.85	7.85	3.91	5.58	4.37	2.77	6.50	10.49	5.15	8.60	5.25	8.32	6.03	7.42
T2	2.05	6.77	1.61	4.27	1.72	4.73	1.56	5.33	2.10	5.25	1.33	4.43	4.64	9.75	1.02	10.06	3.66	9.33	0.99	8.30
T3	5.24	5.17	5.36	10.14	5.59	8.93	6.68	10.02	5.50	7.03	4.67	5.78	5.98	10.81	5.40	10.79	5.40	9.53	5.18	9.81
T4	3.39	6.60	8.11	12.37	3.31	6.72	7.81	12.22	3.50	5.53	7.23	13.33	5.12	5.96	7.49	14.11	4.11	5.24	7.07	12.93
T5	2.68	4.58	2.47	4.10	3.51	5.06	2.72	5.15	3.82	5.08	3.15	4.48	5.20	6.70	3.42	4.42	5.22	6.21	3.39	4.46
	Power spectral density : Theta band ($\mu V^2/Hz$)x10^{-15}																			
T1	172	338	105	235	152	244	94	255	145	262	95	208	124	228	109	356	196	225	166	259
T2	59	120	21	170	44	95	15	164	45	145	17	194	66	232	26	208	82	111	22	457
T3	88	130	47	292	59	102	19	139	43	107	17	171	58	66	27	527	77	424	70	599
T4	37	85	348	468	36	78	169	264	39	91	355	639	30	53	427	621	66	102	267	481
T5	112	379	83	317	197	378	44	148	279	386	47	134	113	261	95	322	364	504	69	303
	Power spectral density : Alpha band ($\mu V^2/Hz$)x10^{-15})																			
T1	116	395	28	92	100	245	26	90	167	366	30	92	262	548	42	175	221	697	53	100
T2	67	348	40	484	65	217	37	393	66	241	62	490	32	295	61	521	203	340	106	1047
T3	109	304	44	493	84	111	22	176	120	178	43	273	87	278	55	332	300	573	97	413
T4	31	52	39	244	14	21	31	137	35	59	56	170	17	44	45	118	38	109	44	255
T5	24	86	11	45	34	136	9	31	45	198	9	27	19	87	14	32	61	235	17	40
	Power spectral density : Beta band ($\mu V^2/Hz$)x10^{-15}																			
T1	7	28	6	37	6	19	5	37	15	48	6	40	16	69	7	27	15	44	11	129
T2	21	93	13	50	22	93	13	50	28	127	18	65	33	258	14	50	50	177	31	84
T3	29	138	10	99	20	103	4	59	33	218	8	113	54	405	13	108	43	339	21	282
T4	3	13	31	111	2	10	31	110	4	14	33	110	3	14	40	118	4	16	22	121
T5	9	47	3	8	9	45	3	6	11	46	3	7	11	46	3	11	15	68	3	7
	Power spectral density : Gamma band ($\mu V^2/Hz$)x10^{-15}																			
T1	0.8	6	3	8	0.5	4	3	7	2	11	3	8	2	14	2	5	0.9	7	5	17
T2	10	46	1	3	11	49	1	3	12	54	1	4	14	59	1	2	14	67	2	5
T3	0.6	3	4	47	0.5	2	2	20	0.8	3	3	33	0.5	3	4	37	0.6	2	6	57
T4	1	3	16	51	1	2	15	52	1	4	19	63	2	4	19	68	2	4	14	52
T5	3	12	1	3	3	15	1	3	3	17	1	4	3	13	2	7	4	19	1	4

QoLS, Quality of Life Scale; DASS, Depression Anxiety Stress Scale; PSYRATS, Psychotic Symptom Rating Scales.

connectivity (**Figure 3C**) revealed a clear higher participation coefficient (represented by the larger green nodes), especially in the left central, left orbito-frontal and the right occipital brain regions. The frontal area showed a relatively lower participation coefficient.

3.2.2. Patient C3

Patient C3 (**Figure 4**) is a woman with paranoid schizophrenia, in the CG, who tool part in the study while taking : aripriprazole, olanzapine, chloroprothixene, and pregabalin. The psychometric outcome (**Figure 4A**) revealed an improvement after the treatment. The quality of life increased, the DASS decreased, while the PSYRATS did not change. The time domain analysis (**Figure 4D**) showed a higher amplitude of the N1-P3 complex after the treatment, except on the temporal regions for the rare stimulus. The PSD (**Figure 4B**) showed higher alpha power post-TMS, except from the right temporal region for both frequent and rare stimuli. The beta band

TABLE 5 | Control Group: Values pre and post treatment of N1-P3, Connectivity, Psychometric and Power spectral density of the frequent (blue) and rare (orange) stimuli(F, frontal; P, parietal; O, occipital; LT, left temporal; RT, right temporal).

	Connectivity				Psychometrics							
	Participation coefficient (%)				QoL		DASS		PSYRATS			
	Pre		Post		Pre		Post		Pre		Post	
C1	29		26		83		84		34		26	
C2	11		15		68		69		52		56	
C3	8		16		41		79		80		42	
C4	13		20		86		78		89		81	
C5	1		22		96		82		11		18	

	Freq				P				O				LT				RT			
	Pre		Post		Pre		Post		Pre		Post		Pre		Post		Pre		Post	
	Freq	Rare	Freq	Rare	Freq	Rare	Freq	Rare	Freq	Rare	Freq	Rare	Freq	Rare	F	Rare	F	Rare	F	Rare
	N1-P3 amplitude (μV)																			
C1	2.94	4.38	2.16	8.27	4.22	4.87	2.71	6.80	2.71	3.09	1.31	7.94	4.61	7.05	0.91	9.58	3.77	6.11	1.49	9.53
C2	8.79	10.26	7.93	10.7	9.54	15.23	8.03	10.98	7.04	7.89	7.67	10.49	5.75	6.22	7.90	14.49	5.84	5.33	7.76	10.88
C3	1.02	3.01	5.16	7.43	2.08	4.59	6.84	8.67	2.01	5.51	5.65	8.42	5.31	11.63	6.89	9.31	5.09	10.61	7.01	9.61
C4	6.49	4.38	1.65	2.15	6.09	5.50	1.63	2.18	5.86	6.83	1.16	1.69	5.97	10.90	1.23	2.01	5.62	10.07	1.22	1.58
C5	5.10	4.71	4.16	2.57	9.16	14.05	4.40	5.72	5.31	5.08	2.62	8.73	8.31	11.93	4.01	13.87	9.00	10.37	4.03	12.49
	Power spectral density : Theta band ($\mu V^2/Hz$)x10^{-15}																			
C1	46	154	68	381	42	146	62	192	45	141	51	195	78	129	59	167	46	118	76	382
C2	647	1651	544	792	245	606	299	289	153	506	188	264	571	1484	156	754	212	1933	311	459
C3	34	42	61	85	29	48	53	79	44	64	73	105	14	86	40	150	80	137	119	102
C4	653	1580	38	175	506	1430	37	190	688	2157	78	216	577	3253	231	328	793	2011	38	225
C5	660	763	429	1919	748	847	281	1543	945	1078	317	1453	1759	1273	1425	3293	1251	1098	200	2306
	Power spectral density : Alpha band ($\mu V^2/Hz$)x10^{-15}																			
C1	34	120	51	215	44	85	35	129	40	116	43	181	46	259	69	174	26	97	45	112
C2	165	849	196	207	97	304	142	156	152	227	174	191	424	563	199	187	162	756	120	325
C3	39	105	79	141	27	94	73	106	34	135	90	153	17	50	130	185	48	345	62	219
C4	139	229	10	73	66	188	10	79	116	238	24	170	306	580	87	391	131	192	10	85
C5	54	177	78	220	57	153	61	218	63	204	77	247	59	340	66	353	55	282	100	347
	Power spectral density : Beta band ($\mu V^2/Hz$)x10^{-15}																			
C1	6	16	9	61	5	17	8	47	5	23	11	58	6	40	18	102	6	24	13	70
C2	18	32	34	29	8	16	21	17	6	19	13	20	17	27	22	43	15	57	28	28
C3	5	11	11	22	5	13	10	22	4	12	12	33	5	10	17	47	5	16	11	23
C4	25	102	4	11	16	60	4	11	23	83	6	23	38	178	14	40	21	76	6	12
C5	8	18	15	58	7	14	12	54	7	14	15	66	7	15	36	190	8	21	10	56
	Power spectral density : Gamma band ($\mu V^2/Hz$)x10^{-15}																			
C1	2	7	3	21	2	5	2	20	3	8	3	21	5	23	6	48	4	9	3	18
C2	8	20	0.5	0.4	6	16	0.3	0.3	6	18	0.2	0.3	9	24	0.4	0.5	8	27	0.3	0.3
C3	3	7	6	24	3	8	6	24	3	9	8	30	6	19	13	42	4	11	5	27
C4	3	19	0.2	2	3	14	0.2	2	4	28	0.2	2	7	41	0.5	8	7	27	0.3	2
C5	2	4	1	7	2	4	1	5	1	4	1	7	2	4	4	13	3	7	1	5

QoLS, Quality of Life Scale; DASS, Depression Anxiety Stress Scale; PSYRATS, Psychotic Symptom Rating Scales.

also showed a higher PSD post-TMS. Finally, the connectivity study (**Figure 4C**) displayed a globally improved participation coefficient, principally in the frontal, occipital, and central areas of the brain.

3.3. Study Case 2 : Stagnation in Psychometric Score

The patient detailed in this section presented a stagnation in her psychometric score post treatment (**Figure 5A**). We chose to describe her in this section in order to find a potential correlation with the neurophysiological data.

3.3.1. Patient C2

Patient C2 (**Figure 5**) is a woman with paranoid schizophrenia, in the CG, who took part in the study while taking : clozapine, flupenthixol, zopiclone, mirtazapine, escitalopram, metoprolol, and chlorpomazine. The psychometric data (**Figure 5A**) showed that the treatment did not have a lot of impact on this scale. The quality of life, the DASS and the PSYRATS remained

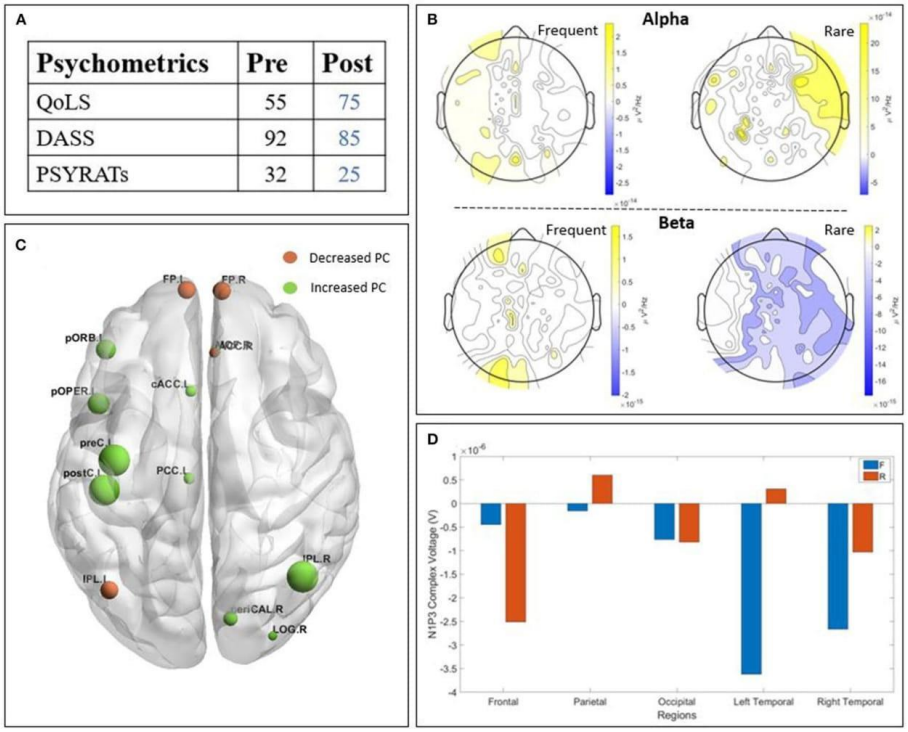

FIGURE 3 | Results of patient T2 : **(A)** psychometric; **(B)** Scalp-level frequency analysis; **(C)** Source-space connectivity; **(D)** Scalp-level time analysis. The yellow areas in frequency analysis are related to a higher Power Spectral Density (PSD) post-treatment, whereas the blue ones are related to a higher PSD pre-treatment. The size of the node in the connectivity is related to the amount of increase (green) or decrease (orange) participation coefficient (PC) values. The positive bars in time analysis are related to a higher N1-P3 amplitude post-treatment. (QoLS, Quality of Life Scale; DASS, Depression Anxiety Stress Scale; PSYRATS, Psychotic Symptom Rating Scales).

more or less the same. The time domain (**Figure 5D**) showed a global increase of N1-P3 amplitude post-TMS, except for the parietal region for both stimuli and the frontal region for the frequent stimulus. The PSD analysis (**Figure 5B**) showed higher alpha and beta power post-TMS (with the exception of frontal frequent stimulus responses in the alpha band). The connectivity analysis (**Figure 5C**) revealed a balanced participation evolution. Globally the left hemisphere (mainly the entorhinal and frontal) showed a decreased participation coefficient, and the right areas (mainly the frontal and occipital) showed an increased participation coefficients.

3.4. Study Case 3 : Decrease in Psychometric Score

The patient detailed in this section presented a decrease in their psychometric score post treatment. We chose to describe him due to his lower values in the neurophysiological data post treatment (**Figure 6A**), in order to find a potential correlation between those two outcomes.

3.4.1. Patient T5

Patient T5 (**Figure 6**) is a man with paranoid schizophrenia, in the TG, who took part in the study while taking : clozapine, flupenthixol, zopiclone, mirtazapine, escitalopram, metoprolol, and chlorpomazine. The psychometric data (**Figure 6A**) showed very little effect of treatment on this scale. The quality of life remained the same, the DASS increased and the PSYRATS slightly increased. The time domain (**Figure 6D**) showed a global decrease of N1-P3 amplitude post-TMS, except for the parietal region for the rare stimulus. The PSD analysis (**Figure 6B**) showed a lower alpha power post-TMS, except for the right temporal region. The beta power decreased as well, except for the right temporal region for the frequent stimulus. The connectivity analysis (**Figure 6C**) showed a globally higher

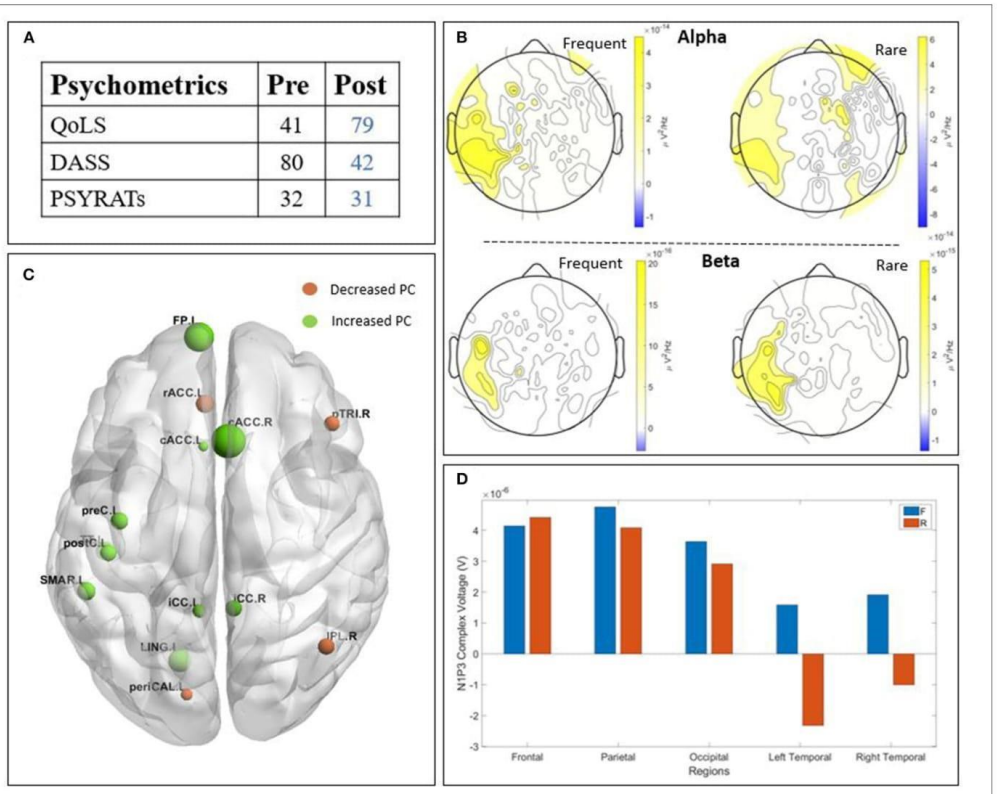

FIGURE 4 | Results of patient C3 : **(A)** psychometric; **(B)** Scalp-level frequency analysis; **(C)** Source-space connectivity; **(D)** Scalp-level time analysis. The yellow areas in frequency analysis are related to a higher Power Spectral Density (PSD) post-treatment, whereas the blue ones are related to a higher PSD pre-treatment. The size of the node in the connectivity is related to the amount of increase (green) or decrease (orange) participation coefficient (PC) values. The positive bars in time analysis are related to a higher N1-P3 amplitude post-treatment. (QoLS, Quality of Life Scale; DASS, Depression Anxiety Stress Scale; PSYRATS, Psychotic Symptom Rating Scales).

participation coefficient in the right frontal, left central, and occipital brain regions.

4. DISCUSSION

The present work aimed to develop hypothesis to assess the effects of TMS in schizophrenia with AVH, analysing EEG data and psychometric outcome. This was based on three different approaches : temporal size (with the calculation of N1P3 complex amplitude), spectral [with the evaluation of the PSD in several frequency bands (theta, alpha, beta, and gamma)] and connectivity, (with the calculation of the participation coefficient in beta and gamma band).

The general results from our study revealed a high variability between individuals, in both groups. This can be explained in several ways : Firstly, subjects were taking a range of medications all of which can interfere with the background neural activity and the generation of ERPs (Javitt et al., 2008). Secondly, the long and tiring recording procedure (around 1 h), and the different states of the patients during the protocol could also have led to varying data quality. Indeed, Polich (1997) highlights the fact that background EEG variation contributes significantly to a high P300 individual variability.

However, there were some indications of improvement in the psychometric results, in four out of five subjects in TG and three out of five in CG. Half of our subjects (six out of 10, four CG, two TG) showed an increase of the N1-P3 amplitude after the treatment, especially for the rare stimulus. Bramon et al. (2004) and Jeon and Polich (2003) established that patients with schizophrenia and AVH presented an inhibition to the P300

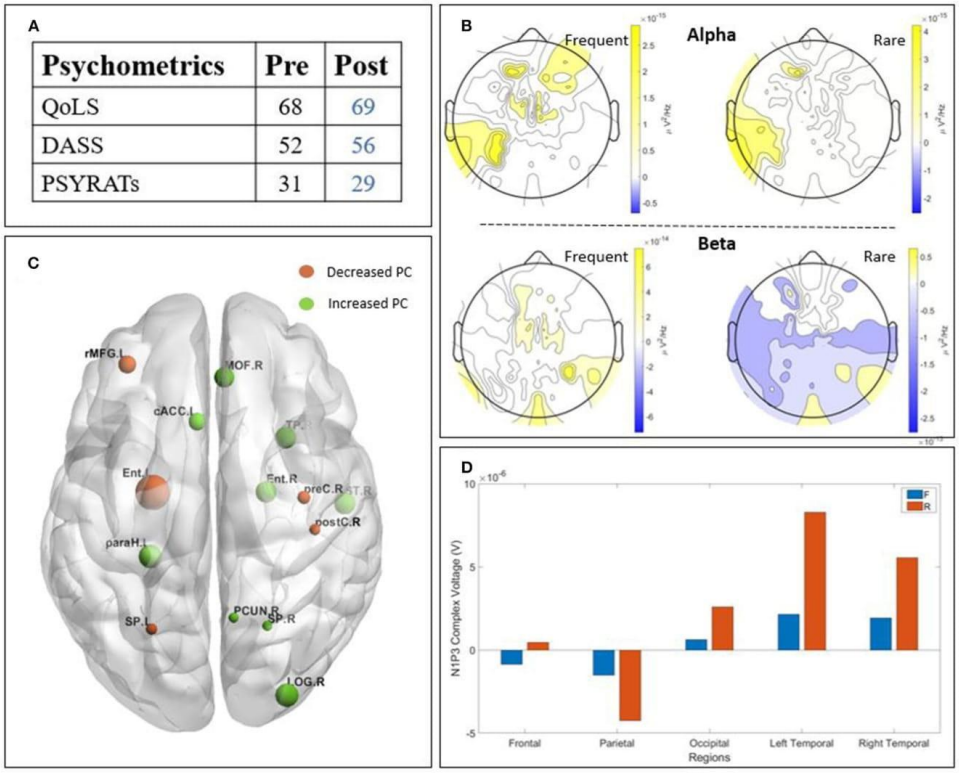

FIGURE 5 | Results of patient C2 : **(A)** psychometric; **(B)** Scalp-level frequency analysis; **(C)** Source-space connectivity; **(D)** Scalp-level time analysis. The yellow areas in frequency analysis are related to a higher Power Spectral Density (PSD) post-treatment, whereas the blue ones are related to a higher PSD pre-treatment. The size of the node in the connectivity is related to the amount of increase (green) or decrease (orange) participation coefficient (PC) values. The positive bars in time analysis are related to a higher N1-P3 amplitude post-treatment. (QoLS, Quality of Life Scale; DASS, Depression Anxiety Stress Scale; PSYRATS, Psychotic Symptom Rating Scales).

experiment. Thus, the clearer presence of N100 and P300 waves post-TMS, which is a known response to the auditory oddball task (Patel and Azzam, 2005), suggested a response to TMS. Likewise, the spectral analysis displayed an increase of the PSD in alpha and beta bands for six subjects (4 in CG, 2 in TG). Ray and Cole (1985) demonstrated that those bands were directly linked to attention, focus, emotional and cognitive processes. A higher power in these bands could be indicative of a change in those mechanisms. Finally, our brain connectivity results showed a global increased participation coefficient in the beta band after treatment, for six subjects (3 in TG, 4 in CG). These results lead us to the conclusion that TMS seemed to have a positive impact on the patients, in both groups. However, it is not possible to assume that the location where the treatment was applied had a different impact on the brain function. The results in connectivity analysis show indeed an improved participation coefficient thus a better network integration independently from the group. Therefore, we discussed the results without regard to the patients' group. We chose to underline in the results section some patients that showed an agreement between the psychometric scores and our neurophysiological data.

It is interesting to note that for patient C3, where the psychometric results were better post-TMS, all three neurophysiological components used for this study revealed a higher value post-TMS. For this patient, there seems to be a clear link between clinical and neurophysiological outcomes. For T2, the trend is there, but is less obvious, with half of the neurophysiological results being in concordance with the improved psychometric score. Conversely, patient T5 had a deterioration in their psychometric

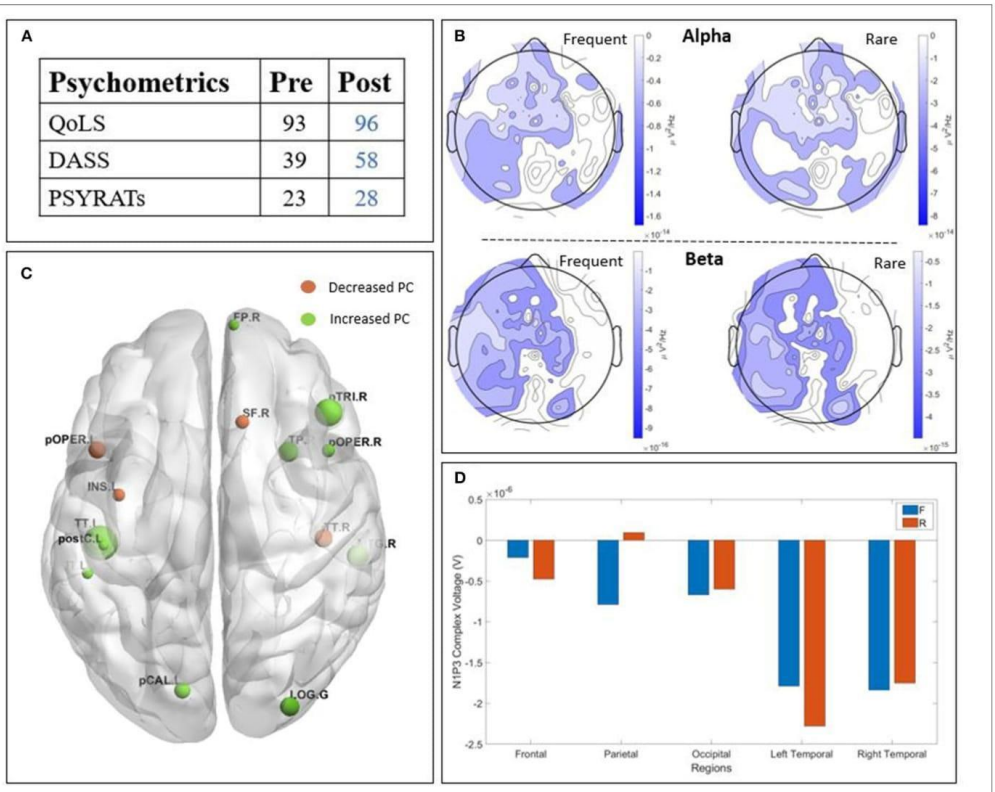

FIGURE 6 | Results of patient T5 : **(A)** psychometric; **(B)** Scalp-level frequency analysis; **(C)** Source-space connectivity; **(D)** Scalp-level time analysis. The yellow areas in frequency analysis are related to a higher Power Spectral Density (PSD) post-treatment, whereas the blue ones are related to a higher PSD pre-treatment. The size of the node in the connectivity is related to the amount of increase (green) or decrease (orange) participation coefficient (PC) values. The positive bars in time analysis are related to a higher N1-P3 amplitude post-treatment. (QoLS, Quality of Life Scale; DASS, Depression Anxiety Stress Scale; PSYRATS, Psychotic Symptom Rating Scales).

post-TMS, and the same tendency is visible in their neurophysiological data,

Although there was significant dissociation between clinical and neurophysiological outcome, the participation coefficient from the connectivity analysis was the parameter that seemed to interact most closely with the psychometric results, followed by alpha power. Concerning the connectivity analysis, our results showed an increased network integration in some brain regions and a slight decrease in other regions, different for every patient. This reconfiguration of the brain network has been widely reported in the literature when stimulating the brain using electrical and magnetic means, and is also present in several brain disorders (Fornito et al., 2015). The increased network integration may be related to better information processing in the human brain and more efficient networks. This increase in network integration was associated with a decrease in this same integration in other brain regions, reflecting the inter-subject variability. Although the small sample size did not allow us to test statistical significance, we showed a clear "trend" of reshaping of the functional brain network between the different conditions.

The frequency analysis revealed the most interesting changes in power spectrum, mainly in the alpha and beta bands. There was higher alpha power post-TMS, which is less prominent but still visible in the beta power. The gamma and theta power did not show any clear trends. The fact that alpha and beta bands are directly linked to attention, focus and emotional tasks (Ray and Cole, 1985) is interesting. A higher power post-TMS linked with a better score in the psychometric scale could indicate that the improvement of these cognitive mechanisms was directly linked to the progress of the patient's clinical condition. Due to our small sample size, this has to be put in perspective, and nothing definitive can be assessed. However, there was a "trend" of an

increase in alpha and beta powers post-TMS that is linked with an improvement in the clinical outcome. Finally, the time domain was the area of analysis presenting the most variability. Half of the patients presented a higher N1-P3, especially in the rare stimuli, but no clear trend was established between this outcome and the clinical outcome. However, due to its conclusive results in studies related to schizophrenia with AVH (Ogura et al., 1991; Ford et al., 2001; Earls et al., 2016), our small number of subjects, as well as its subject inter-variability (Polich, 1997), it is a paradigm that should be taken in account in further studies.

Considering the fact that psychometric tests are a semi-self assessment evaluation of patients condition, this work is a first step toward a development of a hypothesis to correlate and validate psychometrics with quantitative neurophysiological data. We suggest further investigation of any link between psychometrics and neurophysiological data under the umbrella of TMS, focusing mainly on the participation coefficient in the beta band and the power spectral density in alpha band. The beta power as well as the N1-P3 amplitude should also be considered of interest.

4.1. Limitations

The study has many limitations. Firstly, due to the very small sample size, it was not possible to assess our results definitively. Rather, we aimed to discover trends in order to generate hypotheses for further study. Secondly, the patients were also undergoing their usual treatment, including antipsychotic and sedative medications. This did not change between pre- and post-rTMS conditions but might have influenced the background neural activity and the generation of the ERPs (Javitt et al., 2008). Thirdly, the experimental procedure was long (1 h) and tiring and some patients had difficulty cooperating and maintaining task engagement, which may have affected data quality. Muscle and movement artifacts added noise to the EEG signal, requiring a thorough pre-processing and the exclusion of many trials. We encourage similar experiments with patients in the supine position to reduce the noise and improve the data quality, making them easier to process and analyze. Finally, in this study we only analyzed the oddball auditory paradigm. We recommend pursuing this work using other procedures as well, in order to have a more complete overview of the results.

4.2. Future Directives

Future studies of rTMS and neurophysiological markers in schizophrenia should recruit larger number of participants than the present study. The possible association of AVH and other symptoms of schizophrenia with variations in P300, PSD and other EEG markers should be studied further. This may help to establish whether the PSD in the alpha and beta bands, the N1-P3 complex and the participation coefficient in beta bands are reliable biomarkers of the neural response to TMS in patients with schizophrenia and AVH.

5. CONCLUSION

After conducting TMS, most patients showed an evolution in psychometric data as well as on the neurophysiological quantitative data, independent of the stimulation site. We examined the interplay between the psychometric and the neurophysiological data. When the psychometric improved post-TMS, we could observe an increased network integration mainly, through the participation coefficient in the beta bands, a higher alpha and beta band power, and sometimes a higher N1-P3 amplitude. Due to the small sample size, it is not possible to assess definitively the impact of TMS on the brain function in schizophrenia, nor the correlation between psychometric and neurophysiological data. However, our results suggest that brain connectivity, through the participation coefficient, alpha and beta power bands, were highly related with the psychometric score, and that N1-P3, despite his variability, should be investigated. This hypothesis will have to be verified in further studies, with a larger sample size, and an improved recording procedure, leading to a better data quality. This is a first step toward the definition of quantitative neurophysiological parameters to assess TMS treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Health Research Ethics Committee at the University Hospital of Iceland (approval no. 21.2018). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RA and RS wrote the manuscript and performed temporal and spectral group analyses with support from PG. OB, SS, AJ, and EÍ carried out the rTMS treatment. RA, VJ, AJ, EÍ, and OB performed the oddball auditory experiments and HD-EEG acquisitions. OB and EW designed the TMS protocol and made additions to the manuscript. MHas and SY performed the brain connectivity analysis and made additions to the manuscript. MHar and BM designed the psychometrics study. VJ conducted the psychometrics interview. OB and VJ performed psychometrics analysis. DJ reviewed and made additions to the manuscript. OB and PG conceived the original idea and PG coordinated the work. All authors contributed to the article and approved the submitted version.

FUNDING

EW was received support from the Intramural Research Program of the National Institute of Neurological Disorders and Stroke. Landspitali Scientific funds supported this work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2020.575538/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Article III

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Schizophrenia Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

Network signatures of rTMS treatment in patients with schizophrenia and auditory verbal hallucination during an auditory-motor task using HD-EEG

ARTICLE INFO

Keywords
Auditory-motor task
Power spectral density
Graph theory
Schizophrenia
rTMS

To the Editors,

The work we want to describe refers to a simple method of auditory-motor task (AMT) in the EEG evaluation of six patients with schizophrenia (SCZ) and auditory-verbal hallucinations (AVH) receiving repetitive transcranial magnetic stimulation (rTMS).

Disturbances in "functional connectivity" have been proposed as a major pathophysiological mechanism, in particular, for cognitive disorganization (Adhikari et al., 2019). A recent study using functional magnetic resonance imaging (fMRI) in patients with schizophrenia showed that hallucinations severity is related to increased functional connectivity within the auditory and receptive language of the left hemisphere (Okuneye et al., 2020). Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive therapy to reduce AVH severity in pharmacoresistant patients (Slotema et al., 2014). However, a meta-analysis including eleven randomized controlled studies was unable to definitively support or refute the routine use of 1-Hz rTMS in treating AVH in clinical practice (Li et al., 2020). rTMS effects in pharmacoresistant patients with AVH was measured with psychometric scales or questionnaires about AVH (Lefaucheur et al., 2014) and only a few studies were using more objective measurements like fMRI or quantitative electroencephalography (EEG). Vercammen et al. (2010) observed in a fMRI study that 1 Hz rTMS modified the resting-state functional connectivity in patients with AVH at the target site. On the other hand, EEG-related power and connectivity measures were not affected by rTMS in patients with SCZ and AVH (van Lutterveld et al., 2012).

rTMS produces widespread alterations in neural oscillations and functional connectivity measured with EEG during eyes opened resting state. These changes were studied in healthy controls and lasted up to 1 h (Qiu et al., 2020). In patients treated for depression and bipolar disorder rTMS produced a progressive increase in EEG phase locking value during four weeks of treatment (Lebiecka et al., 2018; Zuchowicz et al., 2019).

Resting state EEG studies have been shown to be of a limited value because of the lack of standardized methodology (Newson et al., 2019). Activation tasks are therefore preferable. Studies have shown that evoked (stimulus-locked) and induced (triggered but not locked to stimuli) beta and gamma activity can be elicited during visual discrimination (Lachaux et al., 2000) or auditory cued movement (Nagasawa et al., 2010). Brain connectivity during working memory tasks can be studied with graph theory analysis, especially through the identification of small-world networks (Micheloyannis et al., 2006). Patients with schizophrenia show less local clustering, less hierarchical organization, and signs of disconnection (Micheloyannis, 2012).

We aimed to investigate EEG activity during cognitively driven AMT with ***power spectrum density*** (PSD) and network organization using ***graph-theory algorithms*** in patients with SCZ and persistent AVH before and after low frequency rTMS. In our study we used a methodology described by Nagasawa et al. (2010), who used an auditory-motor task to study performance related changes of cortical gamma and beta EEG activity. We expected that rTMS might induce changes on EEG activity after 10 days of rTMS.

Six patients (mean age = 30.2, SD 2.9, 5 males and 1 female) diagnosed with schizophrenia (SCZ group) and six healthy controls (HC) (mean age = 28.7, SD 4.3, 4 males and 2 females) were included in this study. Most patients were either on clozapine, olanzapine, or poly medicated. The study was approved by the Health Research Ethics Committee of Landspítali University Hospital (Approval No 21. 2018). In the SCZ group, an interview was conducted for the measurement of symptom severity before and after rTMS using PSYRATS auditory hallucinations subscale (Haddock et al., 1999). The healthy participants went through the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1997). Handedness was rated with the Edinburgh handedness inventory (Oldfield, 1971).

A Medtronic MagPro stimulator TMS device and a figure-of-eight coil (MC-B70) were used. Stimulation was delivered at 100% of the resting motor evoked potential threshold for the right *abductor pollicis brevis* muscle, determined before each treatment. The treatment consisted of ten consecutive sessions over two weeks. Each rTMS session lasted 15 min and included 900 pulses delivered at a frequency of 1 Hz. The rTMS was delivered to the left temporoparietal region (T3-P3 EEG location) in four patients or at the vertex (Cz EEG location), in two patients. The analysis was performed for all six patients (SCZ group) as there is not yet

https://doi.org/10.1016/j.schres.2021.06.002
Received 4 May 2021; Received in revised form 11 June 2021; Accepted 13 June 2021

Please cite this article as: Ovidiu C. Banea, *Schizophrenia Research*, https://doi.org/10.1016/j.schres.2021.06.002

a clear support that T3-P3 location is superior in effectiveness to other locations.

Neurophysiological measurements

The EEG for analysis was recorded using 256 channels (ANT Neuro, The Netherlands) during resting state (RS) with eyes opened and during two AMT, each of them with duration of approximately 2 min. The AMT contained 40 trials: 20 auditory-verbal "press" commands and 20 "no press" commands with interstimulus interval of 3 s (Nagasawa et al., 2010). The AMT was performed with the dominant hand (AMT-r) and non-dominant hand (AMT-l) one time in HC and two times in the SCZ patients, before the rTMS treatment (SCZ-T1) and within one week after completing ten sessions of rTMS treatment (SCZ-T2). The raw EEG data of the three different files, RS, AMT-l, and AMT-r were imported for each subject. Channels were located and the sample rate was set at 256 Hz. A bandpass 1–100 Hz filter and 49–51 Hz notch filter were applied, followed by common average re-reference. Artifacts were classified with Independent Component Analysis (ICA) and bad components were semi-automatically excluded using ICLabel (Pion-Tonachini et al., 2019) and SASICA algorithms. For the AMT we defined three epochs in the time-series continuous data as follows: 1) delay epoch (DE) between −2.5 and −1.5 s before "press" and "no press" triggers (Peled et al., 2001); 2) auditory cortical activation (ACA) epoch, from 0 to 500 ms relative to the triggers "press" and "no press"; and 3) motor cortical activation (MCA) epoch, between 0 and 500 ms relative to the button "press".

We selected six regions of interest (ROI) involved in auditory-motor integration to observe the network organization at the cortical level. Each ROI is represented by 17 electrodes. The total number of electrodes was 102 (6 × 17 sensors). The ROIs were selected using MATLAB script as follows: left frontal (LF), left sensorimotor (LSM), left temporoparietal (LTP), right frontal (RF), right sensorimotor (RSM), and right temporoparietal (RTP). The PSD was calculated for each subject in those electrodes that were classified as good, by performing Fast Fourier Transform (FFT)-based analysis using Welch's method with 250 ms Hamming window and 50% overlap for the following frequency bands of interest: alpha (8–13 Hz), beta (13–30 Hz), low gamma (30–49 Hz), and high gamma (51–100 Hz). To describe the network organization using graph-theory algorithms, we calculated the Magnitude Squared Coherence (MSC) between each possible pair of ROIs electrodes into the DE, ACA, and MCA epochs to measure the undirected phase connectivity between the electrodes for each subject (Eq. (1)). We used a 250 ms Hamming window with 90% overlap for each pairwise measure that results in a 102 × 102 connectivity matrix containing all values among the six predefined ROIs.

$$MSC(f) = \frac{|Pxy(f)|2}{Pxx(f)Pyy(f)} \quad (1)$$

A threshold was applied after the creation of the connectivity matrices to remove the connections above and below 0.5 standard deviations of the average MSC of the entire matrix, resulting in significant values that represent the average activity of the scalp network. The significant matrices were then transformed in a directed graph (G) composed of vertices V(G), edges E(G), and weights. The electrodes represent nodes (or vertex), and the connections between phase connectivity measured by MSC represent the edges. The complex dynamic of the scalp-network was described using the number of nodes, number of edges, mean degree centrality, clustering coefficient, characteristic path length, and small-worldness (SW) (Eq. (2)). The SW measures directly the randomness of a complex network. The SW index is calculated by the clustering coefficient (C) and the characteristic path length (L) ratio by size-matched L/L(random) network (Watts and Strogatz, 1998):

$$SW = \frac{C/C_{rand}}{L/L_{rand}} \quad (2)$$

Descriptive statistics are based on median and standard deviation per group and variable. Kruskal-Wallis nonparametric for non-normal data and Two-Way Mixed ANOVA for normal distributed variables tests were performed in each ROI and frequency bands considering the three groups (HC, SCZ-T1, and SCZ-T2) as independent variables. Wilcoxon paired tests were applied as post hoc with a corrected p-value for multiple comparisons in those significantly different frequencies and ROIs for PSD analysis. Dunn's post hoc tests were applied within each group in the network analysis. Non-parametric Kendall's tau-b correlation was also applied to describe the relationships between EEG (PSD or connectivity with graphs) variables and psychometric scales before and after the rTMS protocol. Differences were significant if the corrected p-value was <0.05.

The patients with SCZ showed a significant improvement on psychotic symptoms as measured by PSYRATS AHS between pre-rTMS (M = 28.6, SD = 4.17) and post-rTMS (M = 23.6, SD = 5.27) conditions, $p < 0.05$, $\eta p^2 = 0.967$. However, this might have occurred due to a placebo effect (Li et al., 2020) or a different rTMS target (van Lutterveld et al., 2012).

There were no significant differences of neurophysiological data between HC and SCZ for either auditory or motor epochs. Notably, the SCZ patients showed differences only in a specific epoch of the task - the delay epoch (DE) that refers to the time between the trials, an epoch related to working memory (Peled et al., 2001).

In comparison with the resting state, where we observed differences over both frontal regions (high gamma), both sensorimotor (high gamma), left sensorimotor and left temporoparietal (low gamma) (Table 1), the AMT showed significant differences for both low and high gamma-band frequencies in the "delay epoch" only over the left temporoparietal region (Fig. 1). Compared with HC, PSD was higher in SCZ-T1 and SCZ-T2 while the task was performed with the non-dominant hand. The increased gamma activity was already observed in patients with schizophrenia for the prestimulus baseline period related to working memory or "delay epoch" (Peled et al., 2001) and during cognitive tasks (Gandal et al., 2012) suggesting a workload during this baseline condition. In our study, gamma PSD was higher after rTMS

Table 1
PSD during resting state EEG and AMT during the "delay epoch".

ROI and EEG band	HC[a]	SCZ T1[a]	SCZ T2[a]	HC, SCZ T1, SCZ T2	HC vs SCZ T[b]	HC vs SCZ T2[b]	SCZ T1 vs SCZ T2[b]
Resting state							
LSM							
Low gamma	3,6	10,6	10,83	χ^2 (2) = 7.71, p = 0.021	W: 16, p: 0,016	W: 15, p < 0,01	p > 0,05
High gamma	3,2	10,6	10,17	χ^2 (2) = 9.05, p = 0.011	W: 18, p: 0,05	W: 17, p: 0,017	p > 0,05
RSM							
High gamma	4	10,2	10,33	χ^2 (2) = 6.5, p = 0.03		W: 17, p: 0,017	p > 0,05
LTP							
Low gamma	4,4	7,5	11,3	χ^2 (2) = 6.62, p = 0.036		W: 17, p: 0,017	p > 0,05
AUDITORY MOTOR DE non-dominant hand							
LTP							
PSD low gamma	5,33	10,17	13	χ^2 (2) = 6.32, p = 0.04		W: 24, p: 0,01	p > 0,05
PSD high gamma	5	9,67	14	χ^2 (2) = 8.22, p = 0.016		W: 21, p < 0,01	p > 0,05

DE = delay epoch.
[a] Rank pain score.
[b] Post hoc analysis.

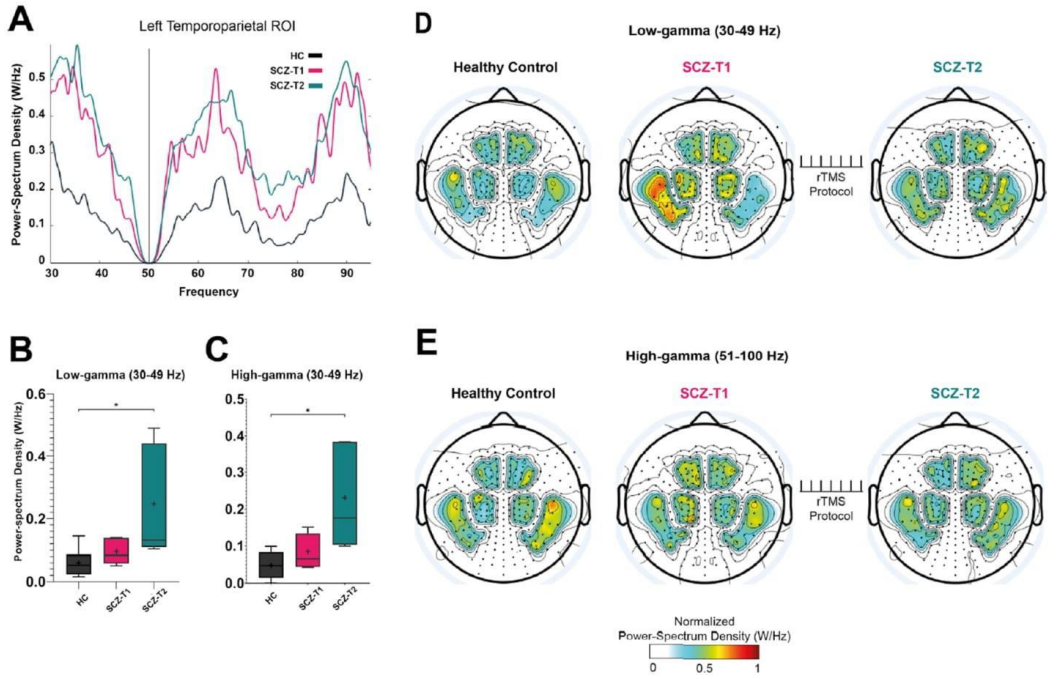

Fig. 1. "Delay epoch" PSD over left temporoparietal ROI during AMT done with non-dominant hand.

suggesting that gamma activity elicited over the left temporoparietal region during the prestimulus "delay epoch" is more prominent when the task requires effort, as it happens when the task is performed with the non-dominant hand. Consequently, we would say that a biomarker of EEG cortical changes would be the increment of gamma PSD after rTMS when the task is performed with the non-dominant hand.

We did not find significant pre-post rTMS differences in any of the analyzed alpha, beta, low gamma, and high gamma bands SW indexes. However, in HC and SCZ-T2 groups when the task was performed with the non-dominant hand, we observed increased path length and reduced SW index of the alpha network. A decreased SW index (more central) was observed for the dominant hand in SCZ-T1. A similar pattern of increased path length and decreased SW was observed for the beta network organization, while the gamma network showed significant differences only regarding the SW. High gamma showed differences for the RS, AMT-r, and AMT-l only in the HC group. Low gamma showed a significant main effect of the condition (RS, AMT-r, and AMT-l) for HC and SCZ-T2 (Table 2), suggesting that rTMS might have influenced the network by restoring the SW index, with the connectivity among nodes in the middle between a completely regular and random network (Watts and Strogatz, 1998).

After identifying that rTMS was able to show the same differences between the conditions in SCZ-T2 that resemble the HC group in low-gamma, we performed the Kendall's Tau correlation to investigate which of these conditions could be related to the improvement of psychotic symptoms after rTMS. Kendall's tau-b correlation showed a strong, negative correlation between the SW of low-gamma phase oscillations of SCZ-T1 and PSYRATS scores, which was statistically significant ($\tau b = -0.788$, $p = 0.032$). On the other hand, Kendall's tau-b correlation showed a strong positive and significant correlation between the same measurements after rTMS (SCZ-T2 group) ($\tau b = 0.733$, $p = 0.039$). This result suggests that the small-worldness phenomenon is correlated with the improvement of psychotic symptomatology after the rTMS in a different way than observed before rTMS (SCZ-T1 group), and this can be a network signature in low-gamma of a possible treatment effect expressed through graph theory and EEG during an AMT

Table 2
Characteristic Path Length and Small Worldness during RS and AMT.

Network organization	Dunn's post hoc	HC		HC		SCZ T1		SCZ T2		SCZ T1		SCZ T2	
Conditions	RS, AMT-r, AMT-l	AMT-r vs RS		AMT-l vs RS		AMT-r vs RS				AMT-l vs RS			
CPL alpha	$F(1, 2) = 13.482$, $p < 0{,}01$, $\eta p^2 = 0{,}442$	↑		↑	$p < 0.01$	↑		↑		↑	$p > 0.05$	↑	$p > 0.05$
CPL beta	$F(1, 2) = 15.347$, $p < 0{,}01$, $\eta p^2 = 0{,}474$	↑		↑	$p < 0.01$	↑		↑		↑		↑	$p < 0.01$
SW alpha	$F(1, 1.235) = 12.614$, $p < 0.01$, $\eta p^2 = 0.426$	↓		↓	$p = 0.02$	↓	$p = 0.02$	↓	$p = 0.04$	↓		↓	$p = 0.04$
SW beta	$F(1, 2) = 15.347$, $p < 0{,}01$, $\eta p^2 = 0{,}474$	↓		↓	$p < 0.043$	↓		↓	$p < 0.001$	↓		↓	$p < 0.01$
SW low gamma	$F(1, 1.037) = 10.774$, $p < 0.01$, $\eta p^2 = 0.388$	↓	$p < 0.01$	↓	$p < 0.01$	↓		↓	$p < 0.01$	↓		↓	$p < 0.01$
SW high gamma	$F(1, 1.030) = 8.528$, $p < 0.01$, $\eta p^2 = 0.334$	↓	$p < 0.01$	↓	$p < 0.01$	↓		↓		↓		↓	

CPL = characteristic path length, SW = small worldness, AMT-r = dominant hand, AMT-l = non-dominant hand.

performed with the non-dominant hand.

Our first limitation is represented by the reduced sample size of our patient group. The patients included in this study received active treatment at T3-P3 or Cz EEG location and this might represent a serious confounding factor. Even so, from the available literature and previous studies, it is not yet defined if the left temporoparietal region is the optimum location for treating AVH severity. Another important limitation is represented by the concomitant medication of the patients which can modulate an abnormal neural oscillatory activity. We encourage further teams working on studies involving the auditory-motor task in patients with schizophrenia, to also include a working memory psychological test as a measure for the cognitive symptoms as the major findings were seen during the "delay epoch", an epoch which is related to the working memory (Peled et al., 2001). In our work we used epochs of 1 s and 0.5 s. A time frequency analysis would be of interest to better define the best EEG bands representation.

This report revealed for the first time that patients with schizophrenia exhibit higher gamma power spectral density between stimuli of the AMT, compared to healthy controls, which was modified by rTMS without being significant. The change of low and high gamma PSD was visible, locally, over the left temporoparietal region, when the task was done with the non-dominant hand, showing that during this condition, gamma synchronization is a marker of "neural effort" and workload during the working memory-related time and not during the auditory or motor cortical activation. SW index of low gamma activity analyzed in patients with schizophrenia and AVH between the auditory stimuli, when it is performed with the non-dominant hand, decreased after rTMS and became similar to SW index found in healthy controls. This might represent an interesting biomarker for rTMS treatment effectiveness.

Role of the funding source

This work was supported by a grant from Reykjavik University A-2020-46, Nr 935931. The patients were given 80 euro and the taxi was paid for the transportation to the treatment unit at the Neurology Department and to the Reykjavik University where the EEG acquirements were performed. Dr. Wassermann received funding from the intramural Clinical Neurosciences Program of the National Institute of Neurological Disorders and Stroke.

CRediT authorship contribution statement

Ovidiu C. Banea, Sigurjón B. Stefánsson, and Eric Wassermann designed the study. Paolo Gargiulo coordinated and guided the work. Viktor Jónasson, with Brynja B. Magnúsdóttir and Magnús Haraldsson, recruited and evaluated the patients. Viktor Jónasson interviewed all patients for PSYRATS auditory hallucinations subscale. Ovidiu C. Banea, Eysteinn Ívarsson, and Aron D. Jónasson performed rTMS treatments. Ovidiu C. Banea, Sara Marcu, Romain Aubonnet, Viktor Jónasson, Eysteinn Ívarsson, and Aron D. Jónasson performed the acquisitions of EEG data during the resting state and auditory-motor task. Ovidiu C. Banea did the preprocessing of the data. Lucas Galdino Bandeira dos Santos and Sara Marcu performed power spectral density analysis, and graph analysis. Lucas Galdino Bandeira dos Santos undertook the statistical analysis. Ovidiu C. Banea and Lucas Galdino Bandeira dos Santos analyzed the literature and wrote the first draft of the manuscript. Ovidiu C. Banea, Lucas Galdino Bandeira dos Santos, Eric Wassermann, Sigurjón B. Stefánsson, Brynja B. Magnúsdóttir and Magnús Haraldsson corrected the manuscript. Paolo Gargiulo revised it and all the authors have approved the final manuscript.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

We thank the patients and their families and the healthy controls who voluntarily participated in this study. We thank Dr. Elías Ólafsson and Mrs. Katrín Einarsdóttir from the Neurology Department of National University Hospital of Iceland for making possible the organization of the rTMS treatments. The authors would like to thank Mrs. Elena Pegolo, Mrs. Sólveig Agnarsdóttir, Mr. Fabio Barollo, Mr. Valerio Gargiulo, Mr. Alec Shaw for the help during the EEG data acquisition at Reykjavik University. Lucas Galdino Bandeira dos Santos would like to offer special thanks for all the guidance, inspiration, and help to Professor Ana Virgínia Moura Ramos, who died in August 2020.

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P50 and P300 Event Related Potentials in Patients with Schizophrenia Recorded from High-Density EEG

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Abstract. The main objectives of this study were to describe P50 and P300 cortical topography in patients with schizophrenia and to define a robust methodology of signal quantification using high density EEG. Within a clinical trial in which patients with schizophrenia and auditory verbal hallucinations were submitted to 10 days rTMS treatment, P50 and P300 were investigated as possible neurophysiological measurements to assess treatment effectiveness together with psychometric scales like Psychotic symptom rating scale (PSYRATS), depression, anxiety and stress scale (DASS) and Quality of Life scale (QoL). Here we describe the technique of collecting P50 and P300 using high-density EEG and we reproduce the preliminary data of P300 in one healthy subject and P50 in two patients and two healthy subjects.

Keywords: P50 · P300 · Schizophrenia · High-density EEG

1 Introduction

Event-related potentials (ERP) provide safe and noninvasive approach to study psychophysiological correlates of mental processes [1]. A meta-analysis confirmed the existence of P300 and P50 deficits in schizophrenia of similar magnitude as findings reported in neuroimaging and neuropsychology [2]. The auditory P300 is a time-locked ERP component indexing attentional resources allocated to the target stimuli and/or the context updating. The P300 peak is defined as the largest positive deflection in the time range from 270 to 470 ms [3]. P50 is a component at the most positive peak between 30 and 70 ms post-stimulus (auditory) onset [4].

J. Henriques et al. (Eds.): MEDICON 2019, IFMBE Proceedings 76, pp. 1071–1077, 2020.
https://doi.org/10.1007/978-3-030-31635-8_130

While the examination of P300 topography in chronically ill schizophrenic and psychotic bipolar patients showed that schizophrenia was associated with a specific left-lateralized posterior abnormality, suggesting underlying posterior temporal lobe pathology with abnormalities of a generator located in the left superior temporal gyrus (STG) [5, 6], the cerebral topography of P50 remains largely unknown [7]. The information processing dysfunction in schizophrenia patients has been associated with a morphological abnormality in the brain [8]. EEG source analysis and the standard paradigm to clarify the neural structures associated with P50 have been used to assess the previously suggested generators of sensory gating. These were found to be STG, hippocampus, dorsolateral prefrontal cortex (DLPFC) and thalamus [9]. In a double auditory stimulus paradigm, the P50 response amplitude of the second (S2) or test stimulus [to that of the first (S1) or conditioned stimulus] demonstrates sensory gating. Deficits in sensory gating are an important endophenotype for schizophrenia [4]. We aimed to describe P50 and P300 in patients with schizophrenia and auditory verbal hallucinations using 256-channel "high-density" EEG. In this work we present data on P300 and P50 topography with signal processing of P300 in one healthy subject and with changes of P50 in baseline conditions from two healthy subjects and two patients with schizophrenia.

2 Materials and Methods

2.1 AVH TMS Clinical Trial in Iceland

The research is part of the ongoing AVH TMS Icelandic project. The goal of this clinical applied research is to assess the effectiveness of repetitive transcranial magnetic stimulation (rTMS) as a treatment of schizophrenic patients with persistent auditory verbal hallucinations (AVH). Sensory gating and cognitive functions using P50 and P300 waveforms are calculated before and after the rTMS treatment. Here we present the preliminary results of P300 topography in one patient and P50 in two patients. Difference of P50 amplitude (S1-S2) and changes of P50 ratio (S2/S1) in baseline conditions of two patients were compared with the results obtained from two healthy control participants.

A total of eighteen patients (range: 18–60 years) will be recruited from the psychiatric wards and outpatient clinics through the National Hospital database of diagnosed schizophrenia patients, following the ICD-10 schizophrenia classification (F20). Only those still experiencing persistent auditory verbal hallucinations after finishing at least two 6–8 week drug prescription treatments will be selected. Permission from the Health Research Ethics Committee at the University Hospital of Iceland was obtained (approval no. 21.2018). P50 and P300 topography in baseline condition for all eighteen patients will be further investigated in two different groups of 9 patients. One group will receive 10 sessions rTMS sham treatment over vertex and the second group will receive treatment with rTMS over left T3P3 scalp location. At the end, baseline conditions will be compared with nine healthy controls.

2.2 EEG Recording and Analysis

The ERP signals were obtained from 256-channel EEG waveguard cap using eego mylab system (ANT Neuro, Netherlands). We grouped the electrodes in seven regions of interest (ROI) with 15 electrodes in each region:

(1) Left anterior L1E-L5E, L1D-L5D, L1C-L5C or 88, 89, 90, 91, 92, 79, 80, 81, 82, 83, 71, 72, 73, 74, 75;
(2) Left posterior L5F-L8F, L6E-L10E, L6D-L9D, L6B-L7B or 102, 103, 104, 105, 93, 94, 95, 96, 97, 84, 85, 86, 87, 69, 70;
(3) Medial anterior L3L-L7L, Z3Z-Z7Z, R3R-R7R or 42, 43 44, 45, 46, 120 121, 122 123, 124, 169, 170, 171, 172, 173;
(4) Medial central L8L-L12L, Z8Z-Z12Z, R8R-R12R or 47, 48, 49, 50, 51, 125, 126, 127, 245, 246, 174, 175, 176, 177, 178;
(5) Medial posterior L13L-L17L, Z13Z-Z17Z, R13R-R17R or 52, 53, 54, 55, 56, 247, 248, 249, 250, 251, 179, 180, 181, 182, 183;
(6) Right anterior R1E-R5E, R1D-R5D, R1C-R5C or 215, 216, 217, 218, 219, 206, 207, 208, 209, 210, 198, 199, 200, 201, 202;
(7) Right posterior R5F-R8F, R6E-R10E, R6D-R9D, R6B-R7B or 229, 230, 231, 232, 220, 221, 222, 223, 224, 211, 212, 213, 214, 196, 197.

The EEG was recorded at a sampling rate of 1024 Hz with an electrooculogram (EOG) electrode placed below the right eye, and a ground electrode placed on the left side of the neck. Electrode resistances were set less than 10 kΩ and referenced to the average of left and right mastoid electrodes (R19R, L19L). The raw EEG was exported and analyzed using Brainstorm [10] and MATLAB 2018b. EEG signals were first notch filtered at 50 Hz, and a later band-pass filter was applied between 0.1 and 80 Hz [11].

P300. In our study P300 response was measured with an auditory oddball paradigm attention task. The recordings were carried out between 11AM and 14 PM. The subjects were sitting in a comfortable chair with their eyes closed. The frequent (F) and the rare (R) auditory stimuli were presented binaurally through headphones at an inter-stimulus interval between tones of constant 1.1 s. For each subject there was 1 trial of 160 tones which will occurred randomly with a probability of 0.2 [12]. We instructed the participants to pay attention at the rare stimuli without counting or moving a finger. The task was performed with eyes closed. The signals were digitized for an epoch of 1000 ms starting 100 ms prior to the presentation of each auditory stimulus (−100 ms to +900 ms). Data analysis was performed with Brainstorm [10] and EEGLAB (v14.1.2b) toolbox of MATLAB 2018b. In this work we present N100-P300 complex signals over the seven scalp ROI of a healthy control participant.

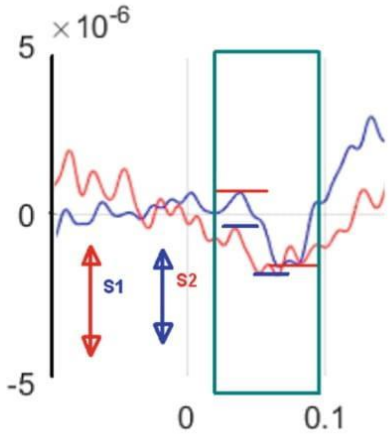

Fig. 1. P50 analysis. Testing stimulus response amplitude S2 (red trace) and conditioning stimulus potential amplitude S1 (blue trace) in 30–70 ms time range are used to determine sensory gating.

P50. The paired-click paradigm was performed to elicit the P50 component. A pure tone (1500 Hz, 6-ms duration) was used as the click sound and presented during a 500-ms interval through headphones. We presented 150 paired stimuli in 5 blocks with interstimulus interval of 10 s, which provided 25 min of EEG measurement. In consideration of participant load and ear comfort that could influence EEG measurement, we instructed participants to watch a silent film. The signals were digitized for an epoch of 500 ms starting 100 ms prior to the presentation of each auditory stimulus (−100 ms to +400 ms).

Individual trials were rejected when EEG voltage was greater than ±80 μV, indicative of excessive muscle activity, eye movements, or other artifacts. We measured the peak-to-peak P50 amplitude from a preceding negative trough to the positive peak at 30–70 ms range from the stimulus onset (Fig. 1). Sensory gating was measured with the difference between testing stimulus (S2) and conditioning stimulus (S1) and the P50 ratio was calculated as the test stimulus response divided by the conditioning stimulus response. For this current study we present data of four participants, two patients diagnosed with schizophrenia and two healthy controls.

3 Results

3.1 P300

The projection of ERP over 256 channel EEG is difficult to quantify and this is one of the limits to measure the rTMS changes on ERPs. To correct this limitation we grouped the scalp electrodes into seven ROI, each region containing 15 electrodes (Fig. 2).

Fig. 2. P300 signals related to the rare auditory stimulus in a healthy control participant (brown). Each N100-P300 complex represents the averaged signal of 15 electrodes. The reorganization of 256 sensors signal into seven regions representing a total of 105 channels might represent an easier tool for P300 amplitude and latency quantification.

3.2 P50

S1 and S2 signals were averaged for the 7 ROI (Fig. 3) in two patients and two healthy controls. S1, S2 amplitude differences S1–S2 (Fig. 4) and S2:S1 ratios (Fig. 5) were calculated. Higher difference of S1–S2 with S1 larger than S2 and reduced S2:S1 ratio explained by reduced S2 amplitude would be correlated with sensory gating.

Patients showed reduced gating in comparison with healthy controls on left posterior, medial anterior and right posterior regions. Left anterior and left posterior regions showed the highest ratio (less sensory gating) in schizophrenia patients in comparison with the healthy controls. Healthy participants showed better response over right posterior or temporo - parietal region (lower value of S2:S1 ratio).

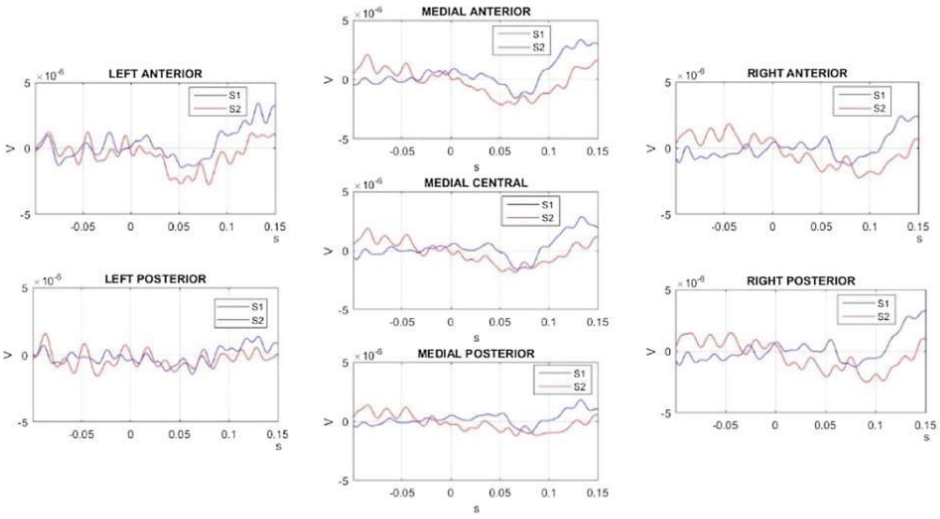

Fig. 3. P50 in a patient with schizophrenia.

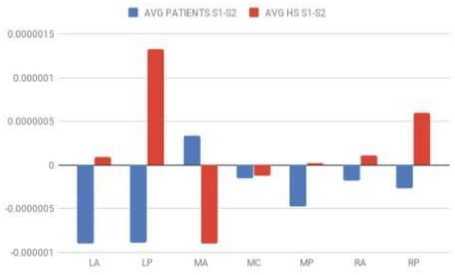

Fig. 4. P50 calculated with amplitude difference S1-S2.

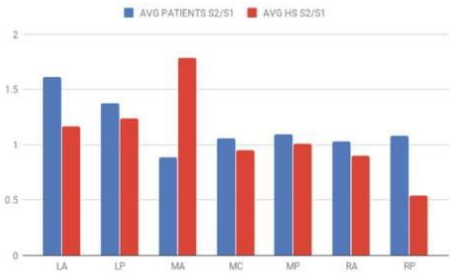

Fig. 5. P50 calculated with S2:S1 ratio.

4 Conclusions

P50 and P300 recorded at scalp level with high density EEG showed high inter-individual and intra-individual variability of signal amplitude, latencies and sensors artifacts. Topographical distribution and best signal localization are serious limits if these waveforms are used for large numbers of participants. Modern quantitative EEG and digitization of signal with large data processing and group analysis might be of interest but component analysis techniques and mixing data of several participants should be carefully considered in order to process all necessary data. To correct these limits we suggested to divide the EEG data in seven scalp regions of interest and we averaged the waves of 15 electrodes for each region. P300 in a healthy control participant showed clear N100-P300 complexes in all seven regions. Preliminary data on P50 analyzed for two patients with schizophrenia showed higher S2:S1 ratio over left anterior and left posterior regions in comparison with the healthy controls suggesting that these regions might be functionally affected.

Greater number of patients and healthy controls will be analyzed following the presented methodology in order to test these assumptions and preliminary results. Further, N100-P300 complex amplitude, P300 latency and P50 S2:S1 ratio will be used as neurophysiological markers to assess rTMS treatment effectiveness in patients with schizophrenia and persisting auditory verbal hallucinations.

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Congress Communication II

A Novel Technique to Trigger High Beta and Low Gamma Activity in Patients with Schizophrenia

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Abstract. The main purpose of this study was to investigate the relationship between resting state and auditory-motor task electroencephalogram beta and gamma distribution in healthy subjects and subjects with schizophrenia. First, we looked to changes in the resting state EEG distribution in three healthy subjects and in three patients with schizophrenia. We also analyzed high-beta and gamma cortical activity from high-density EEG during a cognitively-driven auditory-motor task in two participants, one normal subject and one diagnosed with schizophrenia. For the auditory-motor task, we asked the participants to press a button using the thumb of both hands independently, during two three-minute sessions. Resting state EEG showed more fragmentation in schizophrenia patients when compared with the healthy participants. During the auditory-motor task, we observed increased cortical fragmentation and clustering during the hand response in the patient and healthy control compared with a resting state EEG. The fragmentation remains stable during both hand response time and reference period located between the command "press" and "do not press" suggesting that this task activates a network which remains similar during the entire task.

Keywords: Schizophrenia · Beta activity · Gamma activity · Auditory-motor task

1 Introduction

Neural oscillations are a fundamental mechanism for enabling coordinated activity during normal brain function and represent a crucial target for schizophrenia research [1]. Sensory and cognitive events evoke superimposed and/or parallel oscillations

J. Henriques et al. (Eds.): MEDICON 2019, IFMBE Proceedings 76, pp. 1064–1070, 2020.
https://doi.org/10.1007/978-3-030-31635-8_129

(multiple oscillations) that are transferred to distributed structures with various degrees of intensity, synchronization, duration and delay [2]. In a study with intracranial recordings, auditory-verbal stimuli elicited augmented gamma-oscillations in the posterior portion of the superior temporal gyrus, whereas hand-motor responses elicited gamma-augmentation in the pre- and postcentral gyri [3]. Gamma activity has been investigated in one of the following paradigms: (1) at rest, (2) during "bottom-up" sensory stimulation, or (3) "top-down" cognitively driven tasks [4]. Based on a comprehensive review of the literature, it was concluded that at rest gamma activity is elevated and that task-driven 'evoked' gamma-band responses are reduced in schizophrenia [4].

The aim of our study is to investigate the resting state EEG cortical beta and gamma distribution and if the auditory-motor (AM) task modulates beta and gamma bands activity in healthy subjects (HS) and in patients with auditory verbal hallucinations (AVH). It has been suggested that schizophrenic symptoms can be explained by over-arousal causing depression in neural activity or inverted-U relationship between performance and arousal, also called Yerkes-Dodson Law [5, 6]. Our hypothesis is based on this suggestion and we expect that in schizophrenia the high-beta and gamma activity will break up in clusters and decrease during a task requiring attention, whereas in normal subjects these bands activity will increase.

2 Methods

2.1 Participants

Six participants were selectively recruited through convenience sampling. Three participants (2 male; mean age = 36; range = 30–48) were patients diagnosed with schizophrenia, while the remaining three were healthy controls (2 male; mean age = 26; range = 25–28). Patients were recruited through the National Hospital database of diagnosed schizophrenia patients, following the ICD-10 schizophrenia classification (F20). Only those still experiencing persistent auditory verbal hallucinations after finishing at least two 8 week drug prescription treatments were selected.

2.2 Design and Procedure

An EEG recording was acquired while subjects completed a resting baseline measurement and an auditory-motor (AM) task. The baseline measurement lasted a total of 4 min in two parts: 1 min with eyes closed, and 3 min with eyes opened. A recording was collected for two AM tasks, each lasting three minutes. The participants were awake and comfortably seated in front of a computer screen and were asked to held a button-controller in one hand, with the hand resting on their thigh. During the task,

verbal commands were presented, adjusted to a comfortable volume (Nagasawa et al. 2010). Each subject was instructed to press the button using the thumb when a pre-recorded verbal command saying "press" (*ýttu*) was given, and to not press the button when a verbal command saying "do not press" (*ekki ýta*) was given. Each subject completed the AM task for both hands. The task contained 40 trials; 20 auditory-verbal commands saying "press" and 20 commands saying "do not press", presented in a pseudorandom order, following the latin square method.

EEG Recording and Preprocessing. The EEG was recorded using high-density 256 channel ANT Neuro eego sports system with an electrooculogram (EOG) electrode placed below the right eye, and a ground electrode placed on the left side of the neck. The EEG was recorded at a sampling rate of 1024 Hz. The raw EEG was exported and analyzed using the EEGLAB toolbox (v14.2.2) in MATLAB 2018b. EEG signals were first notch filtered at 50 Hz, and a later band-pass filter was applied between 0.1 and 80 Hz [7]. Eye movements and muscle artifacts were removed by visual inspection. Bad channels were identified by automatic detection using kurtosis, or spectrum measures and later interpolated using the spherical method. The length of the resulting resting state pre-processed data was 40 s ± 10 s for each participant. Finally, the remaining artifact-free continuous data was analyzed.

Data Analysis. First, we analyzed 40 ± 10 s resting state EEG with eyes closed for three patients with schizophrenia and we compared it with the EEG of three healthy control participants. For the auditory motor task, epochs related to the cognitively driven "motor cortical activation" (MCA) were segmented between −500 ms to +500 ms (1000 ms) relative to the onset of the button code (hand reaction) seen in the EEG trace. The reference period was set between +1500 ms to +2500 ms post verbal command or auditory stimulus onset (1000 ms). Finally, the remaining artifact-free trials were analyzed. Here we show preliminary results of motor cortical activation (MCA) for one healthy subject and one patient with auditory verbal hallucinations (AVH), using power spectral density (PSD) and topographical frequency maps including both hands sensory-motor regions. We looked at specific frequencies related to motor reaction: low beta (13–20 Hz), high beta (20–30 Hz), low gamma (30–45 Hz) and high gamma (45–80 Hz). The brain maps showed topographical changes on specific frequencies: 16, 25, 35 and 65 Hz. We compared data with the reference period and with the resting state EEG.

3 Results

Resting state EEG recorded with eyes closed showed topographical and clustering differences of beta and gamma activity between healthy (Fig. 1) and schizophrenia participants (Fig. 2.). In patients with schizophrenia it seems that the EEG is more fragmented. During AM task beta and gamma activity is more visible (higher Z-score)

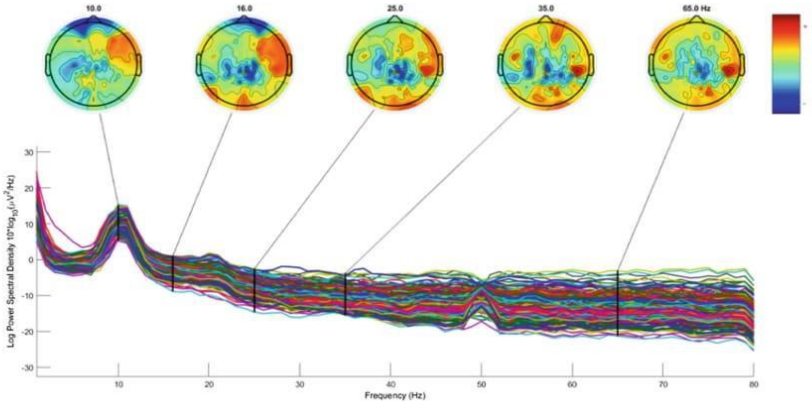

Fig. 1. Power spectral density and specific topographical maps of ***resting state EEG*** averaged for three healthy subjects. 256 channels EEG 40–50 s records with eyes closed.

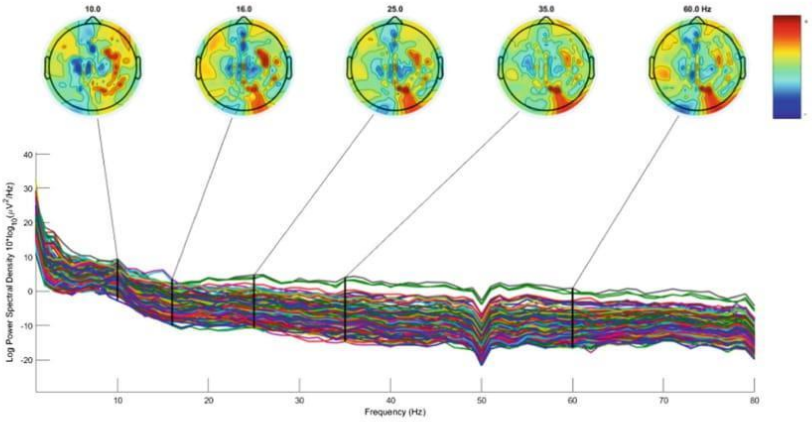

Fig. 2. Power spectral density and specific topographical maps of ***resting state EEG*** averaged for three patients with schizophrenia. 256 channels EEG 40–50 s records with eyes closed.

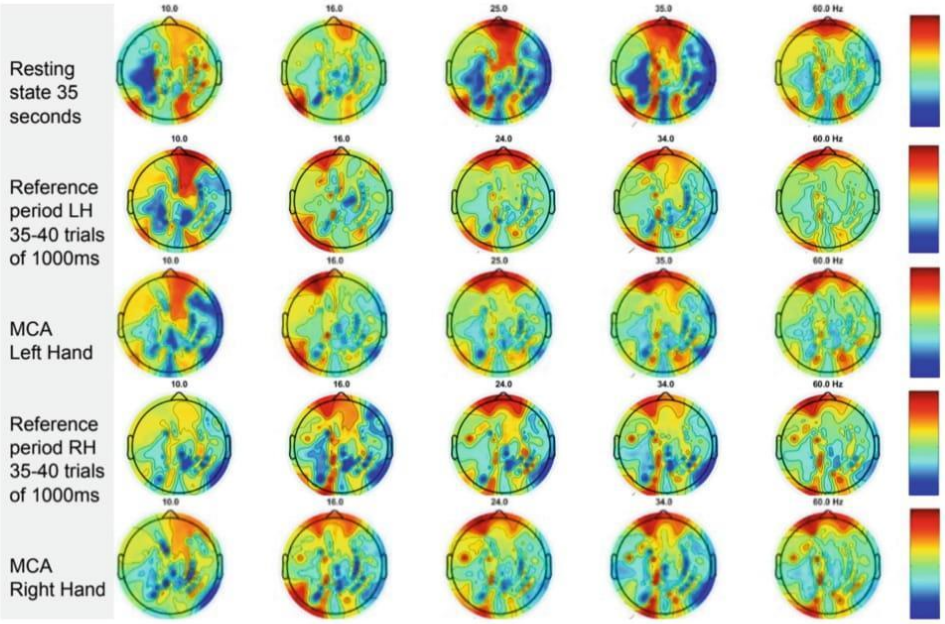

Fig. 3. Auditory-motor task in a healthy participant. Cortical EEG fragmentation is showing similarities between the reference period and hand response during both lateralized tasks. Overall, high beta and gamma activity is reduced during the auditory-motor task.

and more clustered than during resting state EEG for the analyzed healthy participant and this activity remained stable for both bands even during the reference period (Fig. 3). The schizophrenia participant showed reduction of high beta and gamma activity during the AM task, primarily when the task was performed with the dominant hand. The laterality of the cortical activity during left or right hand reaction was not visible (Fig. 4).

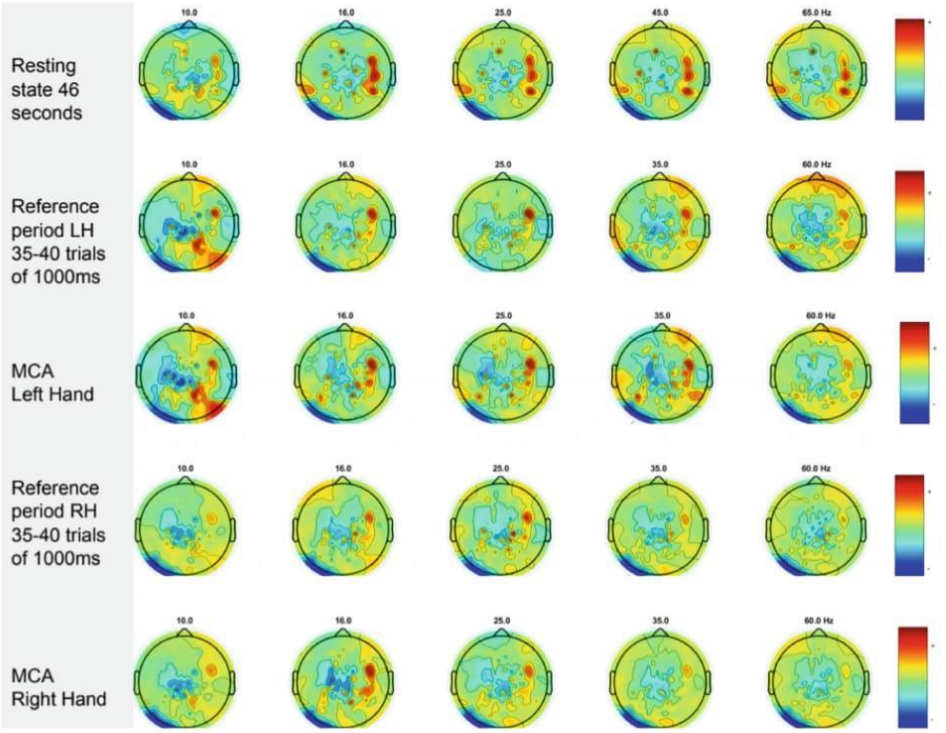

Fig. 4. Auditory-motor task in patient with schizophrenia and auditory verbal hallucinations. Cortical EEG fragmentation is showing similarities between the reference period and hand reaction time during both lateralized tasks. Overall, high beta and gamma activity is reduced during the auditory-motor task.

4 Discussions

The aim of this experiment was to investigate whether there are differences in cortical activity between healthy subjects and patients with schizophrenia during resting state and during an auditory-motor task. Furthermore, we wanted to investigate if the auditory-motor task would modulate beta and gamma activity. Our hypotheses were that: (1) The resting state EEG shows differences of cortical activity in beta and gamma frequencies between healthy control participants and patients with schizophrenia, being more clustered in schizophrenia patients and (2) The auditory-motor task would reduce beta and gamma cortical distribution, compared to the resting state in schizophrenia patient when compared with the healthy control participant. The results are congruent with our hypotheses, showing more clustered and divided cortical distribution in patients with schizophrenia and a reduced activity during the auditory-motor task, even during the reference period between the auditory commands. The activity is stable during the task, with little lateralization effect of the hand responses.

These results indicate that the auditory-motor task triggers a stable network of attention that is held active throughout the task. Cortical activity seemed to be reduced in the schizophrenia participant during the AM task. However, larger number of participants and further analysis with different quantification and clustering methods are needed to test our hypotheses.

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Glossary

electroencephalography	is an electrophysiological monitoring method to record electrical activity on the scalp, or the graphic representation of the brain (In Greek: *encephalon*) electrical activity
graph theory	is the study of graphs, which are mathematical structures used to model pairwise relations between objects
network segregation	is characterized by local information processing, a group of nodes in a module or a region of the brain which are connected, for example, the left hippocampus or the anterior cingulate cortex.
network integration	is characterized by global information processing, by example, interhemispheric connectivity, or the relation between DLPFC and amygdala
working memory	is the small amount of information that can be held in mind and used in the execution of cognitive tasks. Working memory is essential for goal-directed behavior. Impaired WM is a well-documented symptom in schizophrenia and arguably a core feature of the disease. memory that involves storing, focusing attention on, and manipulating information for a relatively short period of time (such as a few seconds)

Acronyms

GABA	γ-amino butyric acid
MLAEP	Mid-latency Auditory Evoked Potentials
EEG	Electroencephalography
PSD	Power Spectral Density
QoL	Quality of Life
DASS	Depression, Anxiety and Stress Scale
PSYRATS	The Psychotic Symptom Rating Scales
DLPFC	Dorsolateral Prefrontal Cortex
CST	Corticospinal Tract

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