Clinical examination of movement disorders

PhD Thesis

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2. ABBREVIATIONS

BDI	Beck Depression Inventory
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression–Severity
CRO	Clinician Report Outcome
DLPFC	Dorso Lateral Prefrontal Cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders 4th edition Text Revision
EQ-5D	EuroQol-5D instrument
ET	Essential Tremor
FTMTRS	Fahn-Tolosa-Marin Tremor Rating Scale
HAM-A	Hamilton Anxiety Scale
HYS	Hoehn-Yahr Scale, Hoehn-Yahr Stage
HRQoL	Health-Related Quality of Life
HRSD	Hamilton Depresszion Rating Scale
Hz	Hertz
KMO	Kayser-Meyer-Olkin value
LARS	Lille Apathy Rating Scale
M_1	Primer Motor Cortex
MADRS	Montgomery-Asberg Depression Rating Scale
MCID	Minimal Clinically Important Difference
MDRS	Mattis Dementia Rating Scale
MDS-UPDRS	Movement Disorders Society–sponsored Unified Parkinson's Disease Rating Scale
MC	Motor Complications (MDS-UPDRS part IV.)
ME	Motor Examination (MDS-UPDRS part III.)
M-EDL	Motor Experiences of Daily Living (MDS-UPDRS part II.)
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
nM-EDL	Non-motor Experiences of Daily Living (MDS-UPDRS part I.)
NMSS	Non-Motor Symptoms Scale
PAS	Parkinson's Anxiety Scale
PDQ-8	Parkinson's Disease Questionnaire -8 items version
PDQ-39	Parkinson's Disease Questionnaire–39 items version
PDQ-39 SI	Parkinson's Disease Questionnaire–39 items version Summary Index
PDSS-2	Parkinson's Disease Sleep Scale 2nd version
PGI-I	Patient-rated Global Impression of Improvement
PGI-S	Patient-rated Global Impression of Severity
PD	Parkinson's Disease
PRO	Patient-Reported Outcome
QUEST	Quality of Life in Essential Tremor
QUEST-SI	Quality of Life in Essential Tremor Summari Index

ROC	Receiver Operating Characteristic
RMT	Resting Motor Threshold
rTMS	repetitive Transcranial Magnetic Stimulation
SMA	Supplementer Motor Area
SD	Standard deviation
SEM	Standard error of measurement
SES	Schwab-England Scale
SF-36	The Short Form (36) Health Survey
TUG	Timed up and go test
Vim	Nucleus ventralis intermedius thalami
UDysRS	Unified Dyskinesia Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale

3. INTRODUCTION

Movement disorders refers to diseases of the central nervous system where the movement is disrupted and/or involuntary abnormal movements occures, while the sensory and primary motor functions relatively well. The most common forms of involuntary movements are tremor, tikk, korea, dystonia, and parkinsonism. In most cases damage to the substantia nigra pars compacta and/or cerebellum is responsibel for the appearence of the symptoms.

3.1. PARKINSON'S DISEASE

Before James Parkinson the Hungarian Ferenc Pápai-Páriz has already described four basic symptoms of the disease: tremor, rigidity, postural instability, and slowless of movement (1). James Parkinson published the disease description first in 1817 (2). The Parkinson's Disease (PD) is the second most common neurodegenerative disorder after Alzheimer's (3). The symptoms of the disease are typical of the older age, but younger patients are becoming more common nowdays (4). PD is slightly common in men and the rate of illness increase with age (5).

The cause of PD is not yet known. Pathophysiologically, decay of the substantia nigra pars compacta dopaminergic cells, and α-synuclein-containing Lewy-bodies appeare at different part of the nervous system.

In addition to genetic factors and mitochondrial dysfunction, environmental factors also play a role in the development of PD. Other predisposing factors may include pesticides, head injuries, air pollution, and certain toxins. Caffeine and high uric acid levels may reduce the chance of PK formation. (3, 6).

3.1.1. Symptoms of Parkinson's Disease

PD is characterized by both motor and non-motor symptoms. The symptoms of the disease are described in *3.1. table*.

3.1. table: *Main symptoms of the Parkinson's Disease*

Motor (motion related) symptoms:	Non-motor symptoms:

• bradykinesia
• rigidity
• tremor
 	
Symptoms typical of advanced phase:
• Posture instability
• Motor complications
  ○ Medication duration shortened
  ○ ON-OFF fluctuation
  ○ Dystonia
	Symptoms typical of early stages
	• Depressive mood
	• Anxiety
	• Sleep disturbance
	• Daytime sleepness
	• Fatigue
	• Pain
	• Concentration difficulty
	
	Symptoms typical of advanced phase:
	• Problems with urinating
	• Salivation
	• Increased sweating
	• Hallucinations
	• Neurocognitive disorder

3.2. SCALES SUITABLE FOR MEASURE PARKINSON'S DISEASE

The symptoms of PD are varied. The most reliable method for characterizing the presence and severity of motor-related symptoms is the physical examination, but the results are not suitable for data processing according to uniform criteria, therefore we use clinical scoring scales that can be evaluated more reliably and objectively.

In the case of PD, the following scales can be validated in Hungarian (7, 8):

- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (9, 10)
- Unified Dyskinesia Rating Scale (UDysRS) (11, 12)
- Parkinson's Disease Sleep Scale 2nd version (PDSS-2) (13, 14)
- Non-motor Symptoms Scale (NMSS) (15, 16)
- Lille Apathy Scale (LARS) (17, 18)
- Parkinson's Anxiety Scale (PAS) (19, 20)
- Mattis Dementia Rating Scale (MDRS) (21)
- Montreal Cognitive Assessment (MoCA) 7.2 and 7.3 version (22, 23)

In the next section, I would like to briefly describe the scales I have used in clinical trials and important for the evaluation of results.

- Hoehn-Yahr Scale (HYS) (24): classify the patients according to severity of motor symptoms (0-5)
- Unified Parkinson's Disease Rating Scale (UPDRS) (25): to measure the severity of PD. The scale has become the standard instrument for PD (26). Its biggest adventage is that it evaluates several dimensions of the PD separately.
- Movement Disorders Society–sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (10): the scale is suitable for the assessment and tracking of motor and non-motor symptoms of PD (27). The Hungariean version of the MDS-UPDRS published in 2013 (9).
- Unified Dyskinesia Rating Scale (UDysRS) (11): measure the extent of dyskinesia damage, spatial appearence, and duration of dyskinesia at the same time. The Hungarian validation publised in 2013 (12).
- Hauser Patient Diary: it can be used to measure the motor fluctuation of PD in time (28, 29).
- Non-Motor Symptoms Scale (NMSS) (15): contributes to the understanding of non-motor symptoms (NMS). The NMSS scale more accurately characterizes NMS symptoms than MDS-UPDRS nM-EDL (30, 31).
- Parkinson's Disease Sleep Scale 2nd version (PDSS-2) (14, 32): based on The Hungarian validation we can speak clinically significant sleep disturbances adove 11 pointss (13).
- Epworth Sleepiness Scale (33): based on the Hungarian validation we we talk about clinically relevant daytime sleepness at score 8 and above (13, 34).
- Schwab-England Scale (SES): measure the patients performance between 0-100% (35).
- Beck Depression Inventory (BDI) (36): focuses on the main symptoms of depression.
- Montgomery-Asberg Depression Rating Scale (MADRS) (37, 38): measure the severity of depression. The test taken by a qualifed professional.
- Hamilton Anxiety Scale (HAM-A) (39): measure the severity of anxiety.
- Clinical Global Impression–Severity (CGI-S): assesses the severity of a particular disease or symptom and the degree of change in treatment effect globally (40) (41, 42).

- Clinical Global Impression-Improvement (CGI-I): characterized by a change since the last test. The scale is taken by a specialist (40, 43).
- Patient-rated Global Impression of Severity (PGI-S): the patient assesses the severity of the disease itself (44).
- Patient-rated Global Impression of Improvement (PGI-I): the patient can describe the change in his/her condition since the previous test (45), (46, 47), (48).

3.3. ESSENTIAL TREMOR

Essential tremor (ET) is one of the most common movement disorders. In contrast to Parkinson's disease, ET occurs mainly during some kind of motion.

Symptoms typically appear in older age (50-60 years), but sometimes occur in younger (20-30 years) ages. By stimulating the Vim core of the thalamus, the intensity of the tremor can be reduced by an average of 70-90%, measured by the Fahn-Tolosa-Marin Tremor Scaling Scale (FTMTRS) (49-51).

3.4. HEALTH-RELATED QUALITY OF LIFE

It is difficult to define the Health-related quality of life (HRQoL).

According to Küchler's model (52), multiple dimensions of HRQoL is exsist (*3.3 táblázat*).

3.3 table: *Basic dimensions of quality of life (53)*

Dimension	Aspects of Quality of life
Physical	Symptoms, side effects, general problems, pain.
Psychic	Cognitive state, emotional state, communication skills, motivation.
Socioeconomic	Housing, work, finance, leisure activities.
Interpersonal	Judgment of the relationship.
Spiritual	Moral values, religiosity.

We can use general and disease-specific scales to assess HRQoL:

- SF-36 (The Short Form (36) Health Survey): used to measure the quality of life, evaluating between 0-100.
- EQ-5D (EuroQol-5D Instrument) (54-60): a non-disease-specific quality of life scale.
- Parkinson's Disease Questionnaire -39/8 items version (PDQ-39/PDQ-8): a specific scale that measures health-related quality of life (61).
- QUEST (Quality of Life in Essential Tremor): Covering 5 different areas: physical symptoms, psychosocial symptoms, communication, hobbies / leisure and work / finance.

3.5. REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Repetitive Transcranial Magnetic Stimulation (rTMS) is a method of modulating the nervous system from the outside of the skull with repetitive magnetic impulses. rTMS can be used as a diagnostic, research and therapeutic tool. Treatment of motor cortex with bilateral rTMS may be effective in treating motor symptoms in PD, while treatment of high frequency left dorso lateral prefrontal cortex (left-DLPFC) rTMS may improve depression associated with Parkinson's disease. (62).

3.5.1. Operating principle of rTMS

The operating principle of the machine is to generate current in the so-called conductive material with a variable electromagnetic field (63).

Two types of coils are used in clinical practice: one is an 8-shaped which form the electromagnetic radiation cone-like, so the pacing will be focused, while in the other circular head, the magnetic field is less focused so we can cover a larger area with pacing (64).

During treatment, we can choose a low (1-4 Hz) or high (5-20 Hz) frequencies, 90%, 110% or 120% intensity of the resting motor threshold (RMT).

3.5.2. Effect of rTMS treatment on depression in Parkinson's Disease

The following table (3.5 table) summarizes the main researches.

***3.5 table**: effects of rTMS on depression in PD*

	Number of patients	Protocol	Main results
1 (Cardoso et al, 2008) (65)	21 PD patients	left-DLPFC rTMS, 15 sec, 50 repeat, 5 Hz 120%, 3 treatments per week for 4 weeks	no improvement in motor symptoms, HRSD and BDI growth
2 (Pál et al, 2010) (66)	22 PD patients	left-DLPFC rTMS, 10 sec., 12 repeat, 20 sec. break 90%, 5 Hz	significant improvement after 30 days
3 (Boggio et al, 2005) (67)	25 PD patients	left-DLPFC, 15 Hz, 110%, 10 repeat	executive functions improved
4 (Fregni et al, 2006) (68)	26 PD patients	left-DLPFC, 15 Hz, 110%, 10 repeat	blood flow growth in DLPFC and anterior gyrus cinguli

*Abbreviations: **PD**: Parkinson's Disease; **DLPFC**:* Dorso Lateral Prefrontal Cortex*; **rTMS**: repetitive Transcranial Magnetic Stimulation; **BDI:** Beck Depression Inventory; **HRSD**: Hamilton Depression Rating Scale*

3.5.3. Effect of rTMS treatment on motor symptoms of Parkinson's Disease

Repetitive transcranial magnetic stimulation is used not only to treat depression but also to influence motor symptoms. Table 3.6 shows the results of researches on PD motor symptoms.

3.6 table: *effects of rTMS treatment on motor symptoms of PD*

	Patients	Protocol	Main results
1 (Hamada et al, 2008; Hamada et al, 2009) (69, 70)	98 PD patients	SMA rTMS: 10 sec. 20 repeat, 5 Hz, 50 sec break, 110%, 8 opportunity	after 12 weeks, there is a demonstrable result in UPDRS III
2 (Siebner et al, 1999) (71)	12 PD patients	rTMS 5 Hz, one-side M1, 90%	decreased the movement time
3 (Sommer et al, 2002) (72)	11 PD beteg	M1 one-side, 1 Hz, 120%, 900 pulses	UPDRS III improved
4 (Rothkegel et al, 2009) (73)	22 PD patients	M1 one-side, 0,5 Hz, 80%, 600 pulses	no detectable change
5 (Siebner et al, 2000; Filipovic et al, 2010) (74, 75)	10 PD patients	M1 one-side, 5 Hz, 90%, 2250 pulses	UPDRS III improved
6 (Khedr et al, 2003) (76)	36 PD patients	M1 bilateral, 5 Hz, 120%, 2000 pulses	UPDRS III improved
7 (Boylanet al, 2001) (77)	10 PK beteg	SMA bilateral, 10 Hz, 110%, 2000 pulses	improve the raction time

*Abbreviations: **PD**: Parkinson's Disease; **rTMS**: repetitive Transcranial Magnetic Stimulation; **SMA**: supplementary motor area; **M1**: primer motor area; **UPDRS III**: Unified Parkinson's Disease Rating Scale Motor Examination*

4. OBJECTIVES

The following objectives have been formulated during clinical trials of motor disorders:

1. In the case of the MDS-UPDRS scale, the result of the merging of parts is becoming more common. We wanted to examine how MDS-UPDRS-based composite scales can be used in the clinic and determine MCID values for these scales. (5. fejezet)
2. The Quality of Life Essential Tremor Scale (QUEST) has not yet been validated in Hungarian. In order to facilitate the diagnosis of the disease, our goal was to validatethe scale to Hungarian. (6. fejezet)
3. By designing a double-blind, randomized, and placebo-controlled study, I aimed to investigate the effects of bilateral primary motor cortex repetitive transcranial magnetic stimulation on motor and non-motor symptoms associated with Parkinson's disease and quality of life related health (7. fejezet)

Since the examined patient populations and the applied methods differ significantly, I present the individual research in a separate chapter.

5. ARE THE MDS-UPDRS-BASED COMPOSITE SCORES CLINICALLY APPLICABLE?

Since the International Parkinson's and Movement Disorders Society–sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (78) has been published, many studies have been used as primary or secondary testing methods in the clinic (78).

The scale is designed to evaluate the individual parts of the clinician separately, but nowadays researches are increasingly widespread where the individual scales are evaluated, so the clinical applicability of MDS-UPDRS composite scales is needed.

In this paper, we examine the applicability of additional composite scales and determine the limit of the minimal clinically significant difference (MCID) following the classical test theory (79).

5.1. MATERIAL AND METHODS

5.1.1. Patients

501 patients participated in the study, each meeting the criteria for UK Brain Bank's Parkinson's disease. 1312 tests were performed. In all cases, we included demographic, medication, and patient related data with MDS-UPDRS validated in Hungarian (9).

5.1.2. Scales

In subsequent studies, the Clinical Global Impression-Improvement and the Patient-rated Global Impression of Improvement were also recorded to measure changes since the previous study (80). In order to ensure the reliability of patient report outcome (PRO) (21) various neurocognitive tests were performed at the first examination to exclude mild to moderate neurocognitive patients (Montreal Cognitive Assessment) (22, 23). The severity of PD is measured by the Hoehn-Yahr Stage (HYS) (81). To compute the composite scales, summed up the individual parts of the scale (MDS-UPDRS II.+III.; MDS-UPDRS I.+II.+III.; MDS-UPDRS total value).

5.1.3. Statistical analysis

When composite scales are created, PRO and CRO (clinician evaluation) measurements should be combined. An independent standard "anchor" is needed to determine both applicability and MCID value, which can be interpreted at the same time (79, 82). If the

Spearman correlation coefficient> 0.3 then the "anchor" and the tested composite scale are suitable for determining the MCID value (79). We choose the PGI-I scale for „anchor”.

For evaluating the usability of PGI-I (79, 83) we calculated the Cohen d value (84). If its value is approximately 0.2, the MCID value is determined successfully (79, 84).

5.2. RESULTS

Due to the presence of a major neurocognitive disorder, 49 patients had to be excluded from the study, thus evaluating from 1113 tests in 452 patients.

Since we created a significant ordinal regression model between the composite scales to be evaluated and the PGI-I (Nagelkerke pseudo-R^2: 0.316, 0.411 and 0.343 for the MDS-UPDRS II. + III., MDS-UPDRS I.+II.+III. and the MDS-UPDRS total value; $p<0,05$), we thought that the results were clinically applicable.

5.3. DISCUSSION

MDS-UPDRS creators do not recommend composite scales but are still used in many studies. Creating composite scales enables more accurate diagnosis of PD, but may weaken test specificity.

Several studies use MDS-UPDRS I. + II. because these tests can measure the severity of PD and problems with PD at the same time.

The composite scale of MDS-UPDRS I. + II. + III. is based on the fact that both the severity of motor and non-motor complications were measured simultaneously with the severity of motor symptoms.

Our goal was to examine whether MDS-UPDRS-based composite scores can be applied to clinical evaluations and to determine MCID values for scales. Our other goal was to examine whether the values of "anchors" (PGI-I, CGI-I) and PRO, CRO could be correlated. We can say that different composite scales can be used, but the MCID limit for independent MDS-UPDRS parts has a better discriminatory feature than composite scales.

6. INDEPENDENT VALIDATION OF THE QUALITY OF LIFE IN ESSENTIAL TREMOR QUASTIONNARIE (QUEST)

Essential tremor (ET) is one of the most common movement disorder in the population (85). The most common symptom in ET is tremor, but recent studies have shown that non-motor symptoms (eg.: sleep problems, depression, anxiety) are also present. (86-88). Clinical diagnosis is based on neurological symptoms (89). The spectrum of symptoms is wide, the range of the disease ranges from mild to severe, which also affects the quality of life in health (HRQoL) (90). In order to reliably characterize HRQoL in ET, we have to apply a questionnaire on quality of life (QUEST) as a disease-specific measuring tool (91) and validate it in Hungarian.

The subject of this study is to conduct an independent validation for QUEST following the Classic Test Theory (92) and set the limit for moderate to severe disease.

6.1. MATERIAL AND METHODS

6.1.1. Patients

In our study, we examined 133 patients who met the system of definite or probable ET criteria. All patients were examined by a neurologist specializing in movement disorders.

6.1.2. Scales

The severity of ET-related problems was characterized by the use of PGI, which evaluates ET as follows: no ET related disease (0), borderline / mild ET-related disease (1), moderate (2), clear (3) and serious ET-related disease that obstructs patients in some of the daily activities (4).

The severity of tremor was assessed by the Fahn-Tolosa-Marin Tremor Rating Scale (FTMRS) (93).

In order to evaluate depression and anxiety, we used Montgomery-Asberg Depression Rating Scale (MADRS) (37, 94) and Hamilton Anxiety Scale (HAS). We used the Montreal Cognitive Assessment (MoCA) to validate the neurocognitive state (22, 23). ET-specific HRQoL was evaluated with QUEST validated in Hungarian (91), (95).

6.1.3. Descriptive data analysis

The value 0 means symptom-free. The occurrence of each element is based on the proportion of patients with> 0. For variables which are following normal distribution (eg.: age, duration of disease) mean and ± standard deviation (SD) were calculated.

6.1.4. Factor analysis

Before factor analysis was used Kayser-Meyer-Olkin (KMO) was calculated. If the KMO is> 0.90 the value is very useful for factor analysis. We only accepted values with a self-value of> 1 and able to do a scree test for factor analysis.

6.1.5. Reliability

A measurement has a high reliability if it produces similar results under even conditions (92). In our study, the internal composition was evaluated in four different ways (95): Chronbach's α (96), corrected batch-to-total correlation, homogeneity coefficient, test retest.

6.1.6. Validity

It depends on how a measurement is well-founded and how accurately it describes reality (92). In this study, structural validity was measured by 3 different methods:

- Convergent Validity: Shows how much a measurement correlates with another predictable measurement (92).
- Internal Validity: Correlation between subscales which can not bo too low (rS <0.300) and can not be too high (rS> 0.700).
- Discriminatory Validity: Indicates whether inseparable concepts or measurements are in fact unrelated (92).

6.1.7. Accuracy

The accuracy of QUEST was estimated by standard error measurement (SEM), where SEM should be less than standard deviation (SD).

6.1.8. Receiver operating characteristic curve

To determine a limit for QUEST-SI that reliably distinguishes between clinically irrelevant and relevant symptoms, we used ROC analysis. The best limit was calculated from the area under the curve for specificity, sensitivity, positive and negative probability ratios.

6.1.9. Statistical analysis

All statistical analysis was performed with IBM SPSS software (version 21.0.1, IBM Inc., Chicago, USA). The significance level was set to 5%. Since the SPSS program was unable to calculate a positive and negative probability ratio, we used a program available on IBM website to calculate it (http://www-01.ibm.com/support/docview.wss?uid=swg21483380).

6.2. RESULTS

6.2.1. Descriptive measurements

Based on the PGI scale, 31 patients (23.3%) did not report any ET problems; 27 patients (20.3%) reported mild, 38 (28.6%) moderate, 22 (16.5%) clear and 15 (11.3%) severe ET problems.

6 patients had 0 at QUEST-SI (4.5%). Some parts of QUEST had a different dominance: part 13 (tremor-induced depression) had the lowest dominance (21.8%), the modul 7 had the highest dominance (meal is disturbed by tremor) (87.2 %).

6.2.2. Factor analysis

The KMO value is sufficiently high (0.914) to perform factor analysis. We used main component analysis extraction method with Virmax rotation, as a result we identified almost the same factor structure as originally.

6.2.3. Reliability analysis

The value of Cronbach's α varies from 0.798 to 0.915 for the parts of QUEST. Each part of the questionnaire reaches the threshold of 0.30. The homogeneity index of each part is acceptable for both the score for each part and for the QUEST-SI.

6.2.4. Validity and accuracy

The internal validity of some parts of QUEST is acceptable (rS values range from 0.300 to 0.700). In terms of discriminatory properties, all sub-scores and total scores differ significantly between depressed and non-depressed, anxiety and non-anxiety. QUEST has an exellent discriminatory validity based on PGI.

6.2.5. ROC analysis

Limit that best separates the existence of a ET-related constraint from the lack of ET-related constraints 11.25. The area under the curve is 0.829 which is the statistical

significance level resulting from ROC analysis ($p < 0.001$).

The limit that best separates the existence of the constraints associated with medium ET is 20.35 points. The area under the curve is 0.731 which is the statistical significance level resulting from the ROC analysis ($p < 0.001$).

6.3. SUMMARY

The aim of this study was to develop the QUEST intercultural adaptation and to evaluate the basic clinicalimetric properties of the scale according to the Classic Test Theory.

Based on a sufficiently high KMO value, the factor analysis performed proved to have almost the same factor structure as that described in the original QUEST study.

The convergent validity between QUEST and other scales was satisfactory. QUEST properly discriminates on quality of life based on anxiety, depression, duration of illness, family history, need for surgery, and PGI.

The authors know that there is no other published study on the limit of QUEST-SI that would distinguish the existence of a clinically significant tremor restriction. Based on the results, QUEST-SI> 11.25 is clinically relevant, where QUEST-SI> 20.35 refers to a severe ET restriction.

6.4. CONCLUSION

Patient feedback and self-test tests are used extensively in the clinic and in research for evaluations, follow-up, and clinical decisions. Validation of clinical scales is important to ensure the accuracy of the measurement in the application environment. Because repeatability is a high scientific requirement, independent evaluation of patient outcomes is essential for confirming or rejecting the results that were created by the scale creators. Our results demonstrate that QUEST, the Hungarian validation, has satisfactory basic clinical properties and confirms the results of the original study. Our thresholds for separating the effects of HRQoL on mild / moderate and moderate / severe ET can also be used in further studies and categorization of ET patients.

7. HIGH-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION CAN IMPROVE DEPRESSION IN PARKINSON'S DISEASE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

There are contradictory datas found on the effect of repetitive transcranial magnetic stimulation (rTMS) on motor symptoms of Parkinson's disease (97). An expert committee set out to unify the effectiveness of rTMS in an evidence-based system (62).

7.1. OBJECTIVE

Since the effect of Parkinson's disease on the rTMS treatment of bilateral high-frequency motor cortex is unclear, a double blind, placebo (pseudo-stimulation) controlled study was designed. We have not only studied the extent of change in motor symptoms and depression, but also changes in health-related quality of life (HRQoL).

7.2. METHODS

7.2.1. Patients

The study included 46 patients with Parkinson's disease (24 men / 22 women, age: 67.4 ± 9.6 years), patients meeting the UK Brain Bank Criteria for for Parkinson's Disease (98), and based on the DSM-IV-TR the criteria of major depression (99) and previously had no rTMS treatment. Patients with mild to moderate depression were identified by an investigator who was not involved in the treatment of patients and scoring for depressive symptoms, resulting in a double blind arrangement.

7.2.2. Test layout

Patients were randomly assigned to an active (n = 23) and pseudo-stimulus (n = 23) group.

The stimulation was performed on the primary motor cortex using a Magstim Rapid 2 (Magstim Inc, Whithland, UK) according to Pascual-Leone and Hallett's instructions (100), with a 70 mm diameter circular head. Strength of stimulation is set to 90% of resting motor threshold (RMT) (stimulation under motor threshold). Patients are treated for 10 consecutive days. The double blind arrangement was further enhanced that who made the treatment did not participate in the patients' health check.

Patients were screened by two Parkinson nurse who did not participate in the treatment and did not know which patient was receiving active or pseudo stimulation. During the treatment, we performed the health check three times to examine the short and long term effects. In order to increase the comparability of results, the patient was evaluated by the same investigator in all three surveys.

Treatment was considered effective if the change was greater than the minimum clinically significant difference. In the MDS-UPDRS Scale Motor Examination part, 3.25 points (101), on the MADRS scale, 1.9 points (102), on the BDI-II scale, 5 points (103, 104), on the PDSS-2 scale, 3 , 44 points (105) and PDQ-39 SI, over 1.6 points (106) were considered clinically relevant.

7.2.3. Statistical analysis

Statistical calculations were performed with IBM SPSS software version 22.0.1 (SPSS Inc, Chicago, IL). We used Friedmann test to evaluate intra-group changes (baseline vs. short and long-term effects), Mann-Whitney test was used to analyze differences between groups (active stimulation vs. false stimulation). In order to avoid the possibility of multiple comparisons, a mixed-order two-way factorial ANOVA was performed.

7.3. RESULTS

Of the 46 patients, 44 completed the study. No side effects or complications associated with rTMS treatment have been observed.

There was no significant difference in baseline parameters for the active and placebo groups.

The masking of the study can be considered effective since 21 (91.4%) from the active group and 20 (95.2%) from the placebo group thought to have received real stimulation ($p = 0.605$, χ^2-test). "Blind" investigators say 9 (39.1%) patients from the active group, and 10 (47.6%) patients from the placebo group received pseudo-stimulation ($p=0,570$, χ^2-test).

7.3.1. Depression

Depression showed significant improvement in both the BDI-II and MADRS scales (*7.2 table,* page 21). Bilateral active M1 rTMS treatment resulted moderate improvement in depression (Cohen's d: 0.724), confirmed by a mixed-order two-way factorial ANOVA test (*7.2 table*, page 21).

7.2 table: *Comparison of changes in the active and pseudo-stimulation group*

	Baseline							Short-term effect							Long-term effect						
	Placebo			Active stimulation			p-value	Placebo			Active stimulation			p-value	Placebo			Active stimulation			p-value
	Median	Interquartile Range		Median	Interquartile Range			Median	Interquartile Range		Median	Interquartile Range			Median	Interquartile Range		Median	Interquartile Range		
MDS-UPDRS Summary Index	53	30	68	52	31	75	0,823	***52***	***34***	***62***	***39***	***28***	***53***	***0,014***	***51***	***33***	***66***	***37***	***26***	***51***	***0,013***
MDS-UPDRS nM-EDL	9	2	14	9	3	16	0,389	8	2	12	5	2	9	0,062	7	2	13	4	2	10	0,091
MDS-UPDRS M-EDL	10	7	17	10	8	14	0,962	10	7	18	8	7	12	0,370	11	10	15	9	7	12	0,268
MDS-UPDRS ME	29	15	41	26	16	46	0,805	***28***	***15***	***34***	***23***	***17***	***37***	***0,048***	***27***	***15***	***35***	***20***	***14***	***31***	***0,019***
MDS-UPDRS MC	3	2	5	2	1	5	0,483	3	2	6	2	0	3	0,054	***4***	***2***	***6***	***2***	***0***	***2***	***0,014***
BDI-II	11	10	15	12	5	18	0,732	***12***	***8***	***16***	***5***	***3***	***10***	***0,004***	***12***	***10***	***15***	***6***	***2***	***10***	***0,001***
MADRS	15	12	17	17	12	20	0,487	***12***	***8***	***17***	***6***	***4***	***13***	***0,010***	***13***	***10***	***18***	***7***	***5***	***12***	***0,003***
ESS	8	4	11	6	4	13	0,962	6	4	9	5	2	10	0,532	8	3	11	7	4	11	0,922
PDSS-2	13	11	21	12	6	30	0,869	12	7	21	7	3	16	0,199	9	5	21	10	7	13	0,972
NMSS Summary Index	64	38	88	68	51	84	0,768	***50***	***33***	***82***	***24***	***22***	***33***	***0,023***	***59***	***39***	***81***	***35***	***22***	***48***	***0,024***
PDQ-39 SI	23,5	15,4	27,7	25,4	18,5	35,4	0,511	***24,6***	***12,2***	***33,4***	***19,1***	***5,5***	***19,7***	***0,045***	***24,2***	***12,9***	***29,9***	***16,9***	***4,5***	***20,0***	***0,014***
MMSE*	29	27	30	29	28	30	0,290	29	28	30	30	27	30	0,218	29	27	30	29	28	30	0,224
MoCA*	21	19	25	26	21	28	0,176	25	23	27	25	22	26	0,943	25	22	29	26	25	27	0,943
Stroop-test: numbr of errors	2	0	4	2	0	5	0,514	1	0	3	2	0	3	0,430	2	0	2	0	0	2	0,757
Stroop test: time	31,1	22,6	45,1	26,7	24,3	40,3	0,078	35,4	26,0	46,7	25,1	18,2	33,6	0,880	26,8	23,9	32,0	25,9	20,0	31,6	0,990
Trail A	41,5	33,0	77,0	65,5	48,0	108,0	0,129	135,5	74,0	213,0	173,0	134,5	316,0	0,080	44,0	32,0	62,0	64,5	50,0	93,5	0,121
Trail B	103,5	80,0	233,0	155,0	112,5	360,5	0,114	40,0	33,0	84,0	61,0	54,0	76,0	0,235	94,0	84,0	229,0	152,5	105,5	238,5	0,320
TUG	11,0	9,2	17,6	11,7	10,0	14,0	0,267	13,3	10,0	18,2	11,0	9,9	14,0	0,185	13,6	10,4	19,0	11,5	8,7	15,0	0,099

Initial value: 1 day before rTMS treatment. Short term effect: 1 day after completion of rTMS treatment. Long term effect: 30 days after treatment. Statistically significant differences are shown in bold. For scales, lower scores mean better clinical status or quality of life, except for those marked with an asterisk, where higher values indicate better clinical status or quality of life. Abbreviations: ***BDI-II****: Beck Depresszió Inventory 2nd version;* ***ESS:*** *Epworth Sleepiness Scale;* ***MADRS:*** *Montgomery-Asberg Depression Rating Scale;* ***MDS-UPDRS****: Movement Disorders Society–sponsored Unified Parkinson's Disease Rating Scale;* ***MDS-UPDRS MC****: Motor Complications (IV. part of thez MDS-UPDRS);* ***MDS-UPDRS ME****: Motor Examination (III. part of the MDS-UPDRS);* ***MDS-UPDRS M-EDL****: Motor Experiences of Daily Living;* ***MDS-UPDRS nM-EDL****: Non-motor Experiences of Daily Living (I. part of the MDS-UPDRS);* ***MMSE****: Mini Mental State Examination;* ***MoCA****: Montreal Cognitive Assessment;* ***NMSS****: Non-Motor Symptoms Scale;* ***PDSS-2*** *: Parkinson's Disease Sleep Scale 2nd version;* ***PDQ-39 SI****: Parkinson's Disease Questionnaire–39 items version Summary Index;* ***TUG****: Timed Up and Go test*

Since both MADRS and BDI-II have had a change (improvement) in the depression that is more than MCID, as a result of bilateral M1 rTMS treatment, the extent of improvement is not only statistically significant but also clinically relevant.

7.3.2. Other non-motor symptoms

There was no improvement in sleep disturbances (PDSS-2 and ESS). No statistically significant change was observed in the first part of MDS-UPDRS (nM-EDL) for non-motor symptoms (*7.2. table*, page 21).

7.3.3. Motor symptoms of Parkinson's disease

Bilateral M1 rTMS treatment showed significant improvements in MDS-UPDRS total score and Motor Examination (Part 3). (*7.2. table*, page 22). The degree of improvement in MDS-UPDRS Motor symptoms improvement is clinically relevant because it exceeded the MCID we determined (3,25 point).

7.3.4. Health-related quality of life

The PDQ-39 Summary Index showed significant improvement as a result of bilateral M1 rTMS treatment (*7.2. table*, page 22). Because it exceeded MCID (1.6 points) (106) the PDQ-39 Summary Index improvement is considered clinically relevant and significant

7.4. DISCUSSION

Many studies have shown the benefits of rTMS treatment in Parkinson's disease, but the current clinical guidelines for its use do not take a stand (107, 108).

In view of the shortcomings to date, a randomized, double-blind, and placebo (pseudo-stimulated) controlled study was designed to measure the efficacy of rTMS treatment on bilateral primary motor cortex in terms of motor and non-motor symptoms associated with Parkinson's disease and quality of lifeAs expected, the remedial effects of bilateral rTMS M1 have been demonstrated for depression and motor symptoms that persisted 30 days after the end of treatment. In addition, we know that we were the first to verify a randomized and controlled study that M1 rTMS treatment significantly improves health-related quality of life. The results can be considered not only statistically but also clinically relevant, although there has been a marked improvement in the treatment effect (MDS-UPDRS ME), depression (MADRS, BDI-II) and quality of life (PDQ-39). the relevant MCID values In addition to depression, other non-motor symptoms have not been shown to have any significant effect.

7.5. CONCLUSIONS

Our study was the first to demonstrate that 10-day left side high frequency (5 Hz) bilateral primary motor cortex rTMS treatment improves health-related quality of life in Parkinson's disease. Improvements in rTMS treatment can also be seen 30 days after treatment.

8. SUMMARY OF NEW RESULTS

These are my results of my research:

- Both our MCID value definition and MDS-UPDRS based composite scales were successful. We can say that pooling the scales on which MDS-UPDRS is based can produce clinically relevant results that can help to better diagnose PD. Our QUEST validation results show that the basic clinical characteristics of the questionnaire are satisfactory and confirm the results of the original study. Our thresholds for separating the effects of HRQoL on mild / moderate and moderate / severe ET can also be used in further studies and categorization of ET patients.
- In a randomized, controlled trial, we first demonstrated that bilateral high frequency primary motor cortex repetitive transcranial magnetic stimulation significantly improves motor symptoms of Parkinson's disease and patients' health releated quality of life.

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10. LIST OF PUBLICATIONS

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