Universitätsspital Basel

Dept. Clinical Neurophysiology/ Neurology

Clinical Study Protocol

Title:
Effectiveness of specific and intensive speech-language therapy on verbal fluency decline and verbal apraxia symptoms in patients with Parkinson's disease with and without Deep Brain Stimulation (DBS) – a randomized single-blind controlled trial.

Acronym: EILT (Evaluation of Intensive Language Therapy)

EKNZ Nr: **2016-01 428**

Clinicaltrail.gov. NR: NCT 029 358 42

Document Created:	30.11.2015
Ethical Approval Obtained:	13.09.2016
Study Start/ First Patient IN:	19.09.2016
Last Patient OUT:	29.06.2018
Study End:	22.10.2018
Final Document update:	**09.10.2019**

Study Synopsis

1. Background and Rationale:	In the course of Parkinson's disease (PD) speech and language (SL) deficits may often emerge. In addition, severe verbal fluency (VF) decline has been repeatedly observed in the context of deep brain stimulation (DBS) in PD. While PD non-DBS patients have deficits with respect to loudness and intelligibility of their voice, PD patients who have undergone DBS (PD-DBS) tend rather to suffer from difficulties in semantic and phonemic word retrieval, and from speech apraxia symptoms. However, to-date and to the best of our knowledge, therapeutic approaches focusing specifically on SL deficits observed in PD-DBS patients are yet to be developed and evaluated regarding their effectiveness.
2. Objective(s):	To evaluate the effectiveness of a high frequency and specific SL therapy compared to an unspecific, non-verbal sham intervention (rhythmic balance-mobility-training (rBMT)), as well as to a 'no therapy'-condition. In more detail: (1) To compare rhythmic speech and gait of PD-DBS and PD non-DBS patients after different intensive rhythmic intervention programs (rSLT, rBMT and no therapy), as well as against healthy controls (HC) directly after the intervention and again in 6 months (short and long-term effects). Secondary objectives: (1) To examine how speech and language abilities alter due to Parkinson Disease's (PD) by comparing PD-DBS, PD non-DBS and HC (all groups are age-, gender and education-matched). (2) To examine the effect of rhythmic interventions on cognitive abilities. (3) To evaluate measures derived from functional Near Infrared Spectroscopy (fNIRS) as a prognostic marker for verbal and cognitive outcome in PD patients with and without DBS over a period of time.
3. Outcomes	Primary study outcome: rhythmic abilities in speech and gait (Velocity and Cadence). Secondary study outcome: • Evaluating the effect of rhythmic interventions on cognition. • Evaluating cortical hemodynamic responses in PD and healthy elderly using functional near-infrared spectroscopy (fNIRS)
4. Study Design:	Investigator-blinded; Randomized; Controlled; Cross-over.

5. Recruitment

Inclusion Criteria for all groups

a) The patient is able to cooperate
b) The patient has the mental competence to provide informed consent to participate in the study
c) The patient speaks and understands German
d) The participants are aged between 45-80 yrs. old.

Specific Inclusion Criteria for the DBS Group

a) Fulfilling the above stated inclusion criteria as stated in a, b, c and d above
b) The patient is responsive to L-DOPA
c) Having received or being scheduled for DBS

Exclusion Criteria for all groups

a) Severe psychiatric disease difficult to treat (compulsive disorder, depression, mania, psychosis, anxiety as outlined in ICD-10 (WHO 2015, current version).
b) Patient with dementia (DMS-V, MMS<24, MoCa <21)
c) Secondary Parkinsonism
d) Age ≤18 years
e) Pregnancy (early onset)
f) Presence of a known disease other than PD that shortens the life expectancy
g) Mental incompetence to provide informed consent to participate in the study
h) Previous intracranial surgery
i) Epilepsy
j) Contraindications for DBS seen in MRI-scan (malignant tumors, severe micro vascular disease)
k) Insufficient skills of German language for participating in neuropsychological evaluations
l) Sensory problems, severe enough to significantly interfere with neuropsychological assessment
m) Alcohol and/or drug addiction

5.1 Number of Participants with Power Analysis:	The intended sample size of N_{total} = 70 is based on a small effect size (η^2=.25, which is statistically significant increase in the elicitation of words within a certain time) and has been calculated via the statistical programme g*power (*power analysis published by the University of Düsseldorf*). Further, we expect about 5 drop-outs. Thus, the intended total sample size (N=70) may compensate for any possible drop-outs, regardless of group type.

6. Randomization

Group 1+2+3 were randomized 1:1:1. As a cross-over designed study, PD patients could swap groups once a therapy- tranche has successfully been completed (i.e. BL, intensive therapy, 4 weeks Follow-up, 6 months Follow-up assessments), see Figure 1.
Group 4 were healthy elderly, who did not receive any therapy and participated once.

Group 1: rhythmic Speech language Therapy (rSLT)
Group 2: rhythmic Balance-Mobility Training (rBMT)
Group 3: '*Waiting List',* PD patients receiving no therapy
Group 4: Healthy Controls (HC)

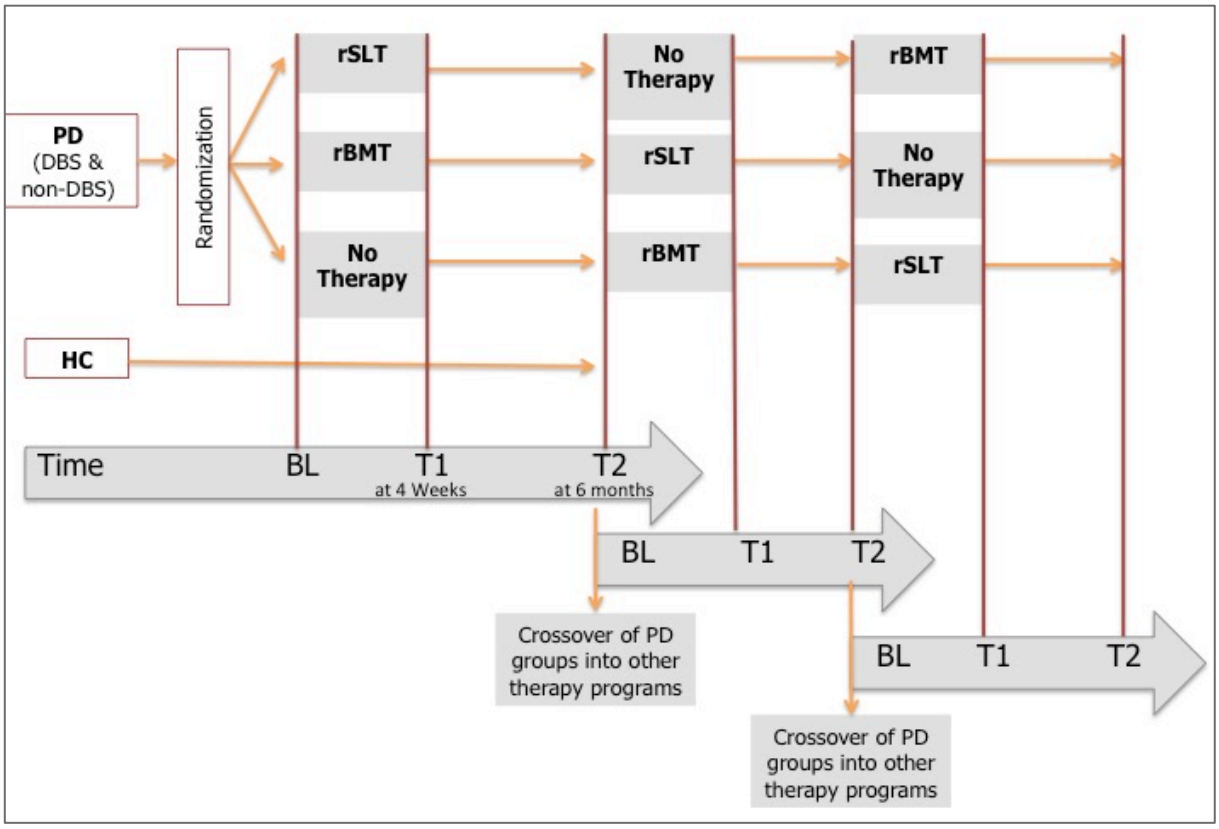

Figure 1. Study Design

7. Testing

Testing took place at baseline (BL), at 4 weeks (T1, directly after the end of intensive treatment) and at 6 months (T2 Follow-up).

a. Medical Examination (only at Baseline)

i. Medical Examination regarding PD-dementia
ii. Drug/Alcohol Abuse
iii. Weight, Heigth, BMI
iv. Medications
v. UPDRS – Unified Parkinson's Disease Rating Scale-I (1/1)
vi. Modified Neurologic Examination according to Hoehn & Yahr
vii. Falls Efficiency Scale-1 (FES-1)

i. Speech-Language Tests with simultaneous PRAAT Recording (BL, T1, T2)

i. Reading 'the northwind and the sun'
ii. Aachner Aphasia Test (AAT): Spontaneous speech
iii. AAT: Repeating
iv. AAT: Naming

v. Regensburgerwortflüssigkeitstest (RWT) complete
vi. Comprehension of language-specific cues (Gardenpath Experiment)

b. Motor Tests

- One-leg and Tandem standing test (timed via chronometric stop watch in seconds)
- Parkinson Orientated Mobility Assessment (POMA)
- Walking 6 Meters (timed and counting steps)

c. Near-Infrared Spectroscopy (NIRS) (only at BL)

d. Neuropsychological tests/ psychiatric questionnaires (BL, T1 and T2)

Neuropsychological Tests:

i. MOCA – Montreal Cognitive Assessement
ii. Clock Test
iii. CERAD – Boston Naming Test
iv. CERAD – Word Retrieval (Animals)
v. BVLT – Basel Verbal Learning Test
vi. BVLT – Basel Verbal Learning Test
vii. ROCF - Rey-Osterrieth Complex Figure
viii. BVLT - Basel Verbal Learning Test
ix. BVLT - Basel Verbal Learning Test - Recognition
x. Word retrieval (S-Words)
xi. TMT - Trail Making Test A
xii. Trail Making Test B
xiii. Stroop Test
xiv. WMS-R - Verbal Digit Span
xv. WMS-R - Corsi Blocks
xvi. Mosaik-Test
xvii. BVMT-R – Brief Visuospatial Memory Test-Revised
xviii. TAP – Alertness
xix. TAP - Divided Attention
xx. Delayed Recall BVMT-R
xxi. Recognition BVMT-R
xxii. Tulia

Psychiatric Self-Rating Questionnaires:

ii. BDI – Beck's Depression Inventory (1/2)
iii. BAI – Beck Angst (Fear) Inventar
iv. MSS – Manie-Selbstbeurteilungsskala (Mania) (1/2)
v. OCIR – Obsessive-Compulsive Inventory-Revised
vi. BIS-11 – Barrat-Impulsiveness-Scale (1/2)
vii. PDQ-39 – Parkinson Quality of Life Questionnaire
viii. NEO-FFi-30 Items

ix. AES-S – Apathy Evaluation Scale
x. PFS-16 – Parkinson-Fatigueskala
xi. Lebensqualitätsfragebogen (SeiQol-DW)
xii. IQ-Code – Questioannaire of cognitive abilites in elderly

8. Interventions

No drugs involved. While speech-language therapy is an established intervention programme in clinical and therapeutic practices, the rhythmic balance-mobility-training (rBMT) has been developed specifically to prevent mobility and balance issues in PD patients and has been evaluated scientifically (*see Parkinson Schweiz* http://www.redance.ch/page/wirkung/sturzpraevention.html*)*.
Note that whether or not DBS is performed on a patient is dependent on multiple criteria and can only be decided by the medical team consisting of neurologists, neurosurgeon and neuropsychologists/ psychiatrists. Whether or not DBS is performed on a patient is not part of the study, as it is a normal medical procedure to cure dyskinesia and other motor symptoms arising in Parkinson's disease.

rSLT		
Contents	I.	3x 45 Minute sessions per week
	II.	Empathic relationship between patient-therapist
	III.	Specific exercises for the perception and improvement of respiration, phonation, articulation and body posture
	IV.	Rhythmic Exercises according to '*Accent Method'* by Sven Smith (1935, 1976)

rBMT	
Contents	• 3 x 45 minute sessions per week. • per session: at least 10 songs had to be danced, each with a length ranging from 1:47 - 3:25 Minutes per song. • 1st Week: Level 1. • 2nd Week: Level 1+2. • 3rd Week: Level 2. • 4th Week: Level 2+3.

7. Statistical Analysis

To calculate group differences (i.e. rSLT, rBMT, NT, HC) several univariate ANOVA with post-hoc Bonferroni corrections were performed.
Relationships between speech and gait variables were computed with Spearman's correlations (significance level $p < .05$). The level of statistical significance was set at $p < .05$.
Changes in performance were analyzed with the reliable change score (RC). According to Jacobson and Truax (1991) scores are compared on a participant-individual level (e.g. BL with 4 weeks FU, and BL with 6 months FU). Positive scores indicate an improvement in performance, and negative scores indicate a worsening of performance. The RC shows whether a difference in performance is statistically significant on the basis of the reliability of the measurement. Thus, the reliable change score is equivalent to computing a z-score based on standard deviation units.
Further group comparisons are based on the RC scores. All statistical analyses were conducted with SPSS and R. All results are presented with effect sizes.

7.1 **Data Availability Agreement**

The Clinical Trail Unit (CTU) of the University Hospital Basel will act as a repository data system. Access to data is granted via formal research enquiry.

8. GCP Statement:

This study has been conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

9. Risks/ Inconveniences, which are study specific:

As Parkinson Patients may suffer from dyskinesia (e.g. rigor, tremor and akinesia), which may affect their movement control and balance, the rhythmic balance-mobility training (rBMT) may potentially put the patients at risk to fall during the intervention. However, there are scaffolds mounted to either side of the rBMT platform, onto which the patient will be holding on to. Furthermore, the research team and therapeutic team will monitor patients during the rBMT as well as the speech-language therapy in order to insure the patients' safety.

10. Benefit for the patient

Through the course of PD patients, both, those who undergo DBS surgery and those who do not, suffer from different degrees of SL performance, which significantly restricts their communication in the society, daily leaving activities and overall quality of life. We anticipate developing and evaluating a possibly preventive or curative therapy considering the patients' SL deficits.
Further, this evaluation will help doctors treating PD patients as well as PD patients to inform (themselves) and choose the therapeutic approach in time regarding the patient's specific needs.

Rationale for the estimated benefit/risk relationship for the patient:

Since the speech-language testing and the interventions per se are non-invasive participating within this study is totally **risk-free** for the patients. Further, there will be no negative consequences whatsoever in case the patient wants to dropout of the study, and dropping-out of the study is possible at any time during the study.
Further, participation in the study will also mean a thorough and fine-grained screening of the patient's health condition (i.e. neurological, neurophysiological, neuropsychiatric and cognitive, etc.). Therefore, this high-frequency screening may allow detecting any concerning health problems early and will be discussed directly (if requested by the patient). In turn, this high-frequency contact with doctors gives the PD patient the rather unique chance to be well informed and ask questions at any time or raise important issues early.
The interventions themselves are unique and specifically tailored to the needs and SL deficits as experienced by the PD-DBS or non-DBS patients. To-date, there is no other intervention program being more up-to-date with the research field than this one presented in this project. Thus, there beneficial effect is not proven. However, the gained insight of their effectiveness will help future PD patients and their neurologists, doctors to give accurate and evidence-proven information about alternative (non-medical) interventions or therapeutic methods,

Selected References:

Batens, K., De Letter, M., Raedt, R., Duyck, W., Vanhoutte, S., Van Roost, D. & Santens, P., 2014. The effects of subthalamic nucleus stimulation on semantic and syntactic performance in spontenous language production in people with Parkinson's disease. Journal of Neurolinguistics. 32: 31-41.

Cantiniaux, S., Vaugoyeau, M., Robert, D., Horrelou-Pitek, C., Mancini, J., Witjas, T., Azulay, J.-P. (2010). Comparative analysis of gait and speech in Parkinson's disease: hypokinetic or dysrhythmic disorders? Journal of Neurology, Neurosurgery and Psychiatry, BMJ Publishing Group, 2010, 81 (2), pp.177.

Ehlen, F. 2007. Effects of subthalamic Deep Brain Stimulation on dysarthria in Parkinson s disease Department of Medicine - Charité - University Medicine Berlin (unpublished Doctorate's thesis).

Ehlen, F., Krugel, L.K., Vonberg, I., Schoenecker, T., Kühn, A.A., Klostermann, F., 2013. Intact lexicon running slowly--prolonged response latencies in patients with subthalamic DBS and verbal fluency deficits. PloS One 8, e79247.

Ramig, L.O., Fox, C., Sapir, S., 2008. Speech treatment for Parkinson's disease. Expert Rev. Neurother. 8, 297–309.

Riecker A1, Mathiak K, Wildgruber D, Erb M, Hertrich I, Grodd W, Ackermann H. 2005. fMRI reveals two distinct cerebral networks subserving speech motor control. Neurology. 22;64(4):700-6.

Sarnthein, J. & Jeanmonod, D., 2007. High Thalamocortical Theta Coherence in Patients with Parkinson's Disease. J Neurosci 27, 124–131.

Skodda S. 2011. Aspects of speech rate and regularity in Parkinson's disease. J Neurol Sci. 15; 310(1-2): 231-6.