

Klinikum der Universität München
Neurologische Klinik und Poliklinik
Direktorin: Prof. Dr. med. Marianne Dieterich
In Assoziation mit dem
Institut für Klinische Neuroimmunologie und dem
Institut für Schlaganfall- und Demenzforschung

Ludwig
Maximilians
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LMU

Application to the ethics committee of the Medical department

Ludwig-Maximilians-University Munich

1. Applicants

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2. Title of the research project

Introvision in migraines and headaches - IntroMig

3. Training data and research experience of applicants

Dr. Med. Monika Empl was born on 06.02.1970. From 1990 to 1997, the applicant completed her studies in human medicine at the Ludwigs-Maximilians University in Munich. From 1997 to 2007 she worked as Assistant doctor at the neurological department of the Ludwigs-Maximilians-University, since 2007 she has been a consultant in neurology at the Ludwig-Maximilians-Universität in Munich. She completed two research visits (1999: Cantonal Hospital Basel, Prof. Andreas Stecker: Painful neuropathy, 2002/2003: National Hospital for Neurology and Neurosurgery, Prof. Peter Goadsby, London: NOx in Cluster headache patients). In 2009 she completed the medical investigator course. She has previously been involved in many headache studies as a investigator and is currently investigator in several headache studies (CGAL/CGAM: CGRP antagonist at episodic (CGAL) and Chronic (CGAM) cluster headache; non-invasive vagus nerve stimulation for episodic Migraine (GM-11 GammaCore-R for the prevention of episodic migraine), Chordate PM004 (novel attack treatment of migraine by mechanical stimulation of the nasal mucosa) and from autumn 2015 AMG 334 for migraines.

Mr. Prof. Dr. Med. Andreas Straube (9.5.1958) studied at the University of Bochum and Essen. He gained his approbation in 1985, Doctor of Neurology in 1991, Habilitation 1993, 1993 to 1998 Heisenberg Fellowship of the DFG, appointment to a C3 Professorship 1998, 2004 special Pain Therapy. Head of the Upper Bavarian Headache Center since 2006. Research focuses on headache, neuro-oncology and Okulomotorik. Prof. Straube was a long-time spokesman for a DFG-graduate college and multiple applicant for DFG, Fresenius-Stiftung and Humboldt-Stiftung. Participation in multiple national and international studies.

Ms. Prof. Angelika C. Wagner studied pedagogy (Bonn/Hamburg) and Psychology (Southern Illinois University Carbondale; University of Michigan, Ann Arbor). She is currently Prof. emerita for Pedagogical psychology at the Department of Educational Science and has developed the method of Introvision together with the theory of mental introference and the theory of subjective imperatives, within the framework of a long-term research programme, in many empirical studies, including a BMBF-sponsored project (1). Under her guidance, several studies on the efficacy of Introvision have already been carried out, including in neck tension (2,3), tinnitus (4), improvement of sports performance (sailing (5), reduction of asthmatic discomfort, dissolution of vocal blockades

for singers, burnout prevention (for the last four areas is the source: www.ew.uni-hamburg.de/de/ueber-die-fakultaet/personen/wagner-ang.html). Currently there is also a cooperation with another empirical project of Introvision in cooperation with a Transregio-SFB on sleep research (Prof. Dr. Junghanns from the University Clinic in Lübeck, which deals with the effects of Introvision on the reduction of stress among high school students.

4. Multicentre studies

n.a.

5. Declaration on the Helsinki Declaration

The declaration of Helsinki, according to the amendment of Summerset west of October 1996 and the previous amendment, is considered.

6. Study-related burdens

In the course of the study, no study-related radiation exposure is created for the participants. Furthermore, no diagnostic tests and samples (blood, liquor or tissue) are carried out within the scope of the study.

7. Scientific information on the research project

7.1.1 Background/Current State of knowledge:

Introvision is a mental self-regulation in order to resolve mental blockages and thoughts that arise through (unconscious) internal conflicts and thus reduces stress. Introvision was developed (1) by Prof. A. C. Wagner, University of Hamburg, within the framework of a long-term research program for mental self-regulation and the dissolution of internal conflicts. The Introvision aims at the resolution of internal conflicts with the technique of descriptive attentive perceiving (KAW), a mindfulness technique. The background of the Introvision is the theory of mental Introference as well as the theory of subjective imperatives. These theories describe how an initial hang of the thought process in an inner conflict is operationalised by subjective intended notions (subjective imperatives) so that an inner tension/stress arises in a similar situation. The degree of inner tension can vary and go from mild stress to total thought-block (black-out) or permanent thought circles.

For example, in the uncertainty about the correct spelling of a word: when the thought process hangs (epistemic system) in search of the correct spelling there are several possibilities: 1. Looking for the correct spelling (i.e. in a dictionary) results in no conflicts for the thought process (epistemic system). The solution of the problem is registered correctly, no tension is created.

2. One chooses a probably correct spelling. However, the uncertainty about the correct spelling remains and the epistemic system is aware of the uncertainty. Dealing with this uncertainty, corresponds to an internal conflict, the degree of which can vary and depends on the situation/personality or the subjective imperatives: in an important letter such as an application or an examination, uncertainty results in an emotional tension can certainly be felt more clearly, since in such situations often subjective imperatives such as "I must not fall through the test" or "I must get this place" occur. You can also displace the idea of the correct spelling, or you always return automatically, or you keep assuring yourself that you have written correctly, or that it is not so important. All these thought processes cost mental energy in the thought process and can also cause mental blockages when the situation recurs.

With Introvision, an attempt is made to gain access to the unconscious intended thoughts and ideas through an attention technique (KAW: descriptive attentive perception (subjective imperatives), and then to decouple these thoughts and ideas from the connected negative emotions, similar to the approach in trauma therapy.

There are already studies on the efficacy of Introvision in chronic neck tension (2) and tinnitus (3). The efficacy was clearly demonstrated three months after treatment with Introvision (4).

The advantage of this technique is that it is not very expensive in comparison with psychotherapy, dissolves the tension from the root and only requires a limited use of therapists, so it could also be used in the accompanying therapy of headache disorders.

1.3 Need to conduct the clinical trial

Migraine is a neurological disorder which is classified by the WHO as one of the 10 diseases with the highest impairment of quality of life and high socio-economic costs (estimated for Germany: €17 billion/year with annual individual costs for a migraine patient of €1200/year) (6). In patients with frequent migraine attacks or chronic migraines, stress is a well-known and regularly existing trigger factor (7). Recognized relaxation methods in migraines and headaches, such as progressive muscle relaxation after Jacobson or biofeedback, temporarily reduce tension, but do not dissolve the tension. In order to check whether Introvision in patients with frequent migraine attacks or chronic migraines is effective in reducing headaches, a study at the Upper Bavarian Headache Center, Ludwigs-Maximilians University of Munich, in collaboration with the University of Hamburg is conducted.

7.1.2 Question/Study Objective:

Is Introvision effective in reducing headache days per month (primary target, documented in the headache diary) compared to waiting list group, reduction of the intensity of headache, reduction of

acute medication, burden of Headache (Headache Impact test-6), participants improve in a self-efficacy test for headaches (HMSE-short version).

7.2 Type of Study

Name and justification of the type of study: monocentric randomized waiting list control study. ('Investigator-driven').

7.2.1 Research projects with potential benefits for the participant

The study participants learn the technique of Introvision with descriptive attentive perception, retrospective thinking, recognition of subjective imperatives as well as the theoretical background of the Introvision in 6 group sessions with up to 10 participants and then receive three sessions of accompanied Introvision by experienced Introvisions consultants to dissolve the mental blockages. It is possible that the frequency and intensity of migraines is significantly reduced by the Introvision and the technique of the Introvision for mental self-regulation/stress reduction also offers a benefit for the participants in further life.

Study participants can continue to treat their headache attacks as usual. It is only required that no new/additional drug or non-drug measures be taken to prevent headaches.

7.2.2 Research projects without potential benefits for the participant:

n.a.

7.2.3 Research on body materials/tissue collection for study purposes:

n.a.

7.3 Study design, duration of study, case number estimation

It is a mono-centric randomized waiting list control study. The purpose of the study is to examine patients who meet the following inclusion criteria:

Inclusion criteria:

1. Patients with a mimimum age of 18 years
2. Episodic migraine diagnosed according to IHS 3 Beta with at least 5 headache days per month, episodic migraine and episodic tension headache (min. total of 5 migraine headache days) or chronic migraine (more than 15 headache days per month, of which at least 8 migraine days since 3 months).
3. Stable headache preventive medication

4. Stable non-drug prevention measures (e.g. regular endurance sports)
5. Written informed consent of the patient

Exclusion criteria:

1. Indication of another symptomatic headache cause
2. Other headaches or facial pains (cluster headaches, trigeminal neuralgia, idiopathic facial pain, new persistent daily headache)
3. Manifest severe depression (BDI-FS > 13 points)
4. Drug or alcohol addiction
5. Lack of compliance, especially for documentation in the Headache diary

After information and consent, patients are randomized into the experimental group or waiting list group. The experimental group fills in a headache diary for a minimum period of one month without waiting, otherwise a headache diary of at least 1 month is to be completed, the waiting list group starts after a waiting time of at least 6 weeks, to attend 6 group meetings with a maximum of 10 participants, in which the background of the Introvision is explained, the technique of descriptive attentive perception and the detection of subjective imperatives is taught, also with the help of standardized presentations. Participants will then receive 3 individual sessions, via video conference with experienced Introvisions consultants from Hamburg. Participants are asked to fill in a headache diary throughout the entire course of the study up to 3 months after the Introvision, with documentation of the number of headache days and intensity of the headache (weak, medium, strong), as well as the documentation of the days with pain medication ingestion and frequency of Introvisions exercises.

The study is expected to begin in December 2015. Patients should be recruited via the neurological outpatient clinic as well as advertisements.

With an estimated average headache frequency of 10 +/- 5 days per month, a 50% reduction in headache is estimated. With an assumed reduction to 5 headache days per month in the experimental group and 8.5 days per month in the waiting list group, an expected difference (effect) of 3.5 +/- 5 days per month for a two-sided 5% significance threshold, a 1:1 randomization and a statistical power of 80% (calculated by a T-test for independent samples) a case number of 33 per group and a total of 66 patients is calculated. Depending on the distribution of the values, the final evaluation of the data can also be done non-parametrically using man-whitney-U test. The case number estimation was carried out by Dr. Eva Hoster, Institute for Biometrics and Epidemiology, LMU Munich.

In the neurological clinic, significantly more than 750 headache patients are treated every year. If 2-3 patients per week are recruited, 26 or 33 weeks are needed to recruit the full number of

participants. Together with the evaluation of the primary parameter after 5 months, one can assume a study period of 1 to 1.5 years.

As part of the study, the following information is documented.

- Name, first name, date of birth, age, sex of the patient
- Number and intensity of headache days per month, documented in headache diary
- Number of days taken with acute medication for headaches, documented in headache diary
- Beck-Depression-Inventory: fast-screen for documentation of mood situation
- Questionnaire on self-efficacy in the case of headaches (HMSE-short version)
- Number of KAW exercises per week (0-1, 1-3, > 3)
- Satisfaction of the participants with the treatment
- HIT-6 questionnaire (headache-impact-test) to assess the impact of the headache

In addition to determining the primary parameter (reduction of headache days per month in the 3rd month after the Introvision) compared to the headache days per month of the waiting list group after the waiting period, as secondary parameters the Introvision effect will be evaluated in both pooled groups as well as the influence of the frequency of KAW exercises and the self-assessment of the efficacy of the Introvision after completion of the Introvision. In addition, the satisfaction of the participants with the treatment and an assessment of the Introvision consultants of the mastery of the Introvision of the respective patient is documented.

8.1. Discussion of the ethically/legally relevant issues

According to previous experience with comparable study designs, we do not expect any lasting psychological burdens for the participants of the study. There are no risks to the physical health of the participants. The participants are informed in detail in writing and orally about the aims and procedure of the study. The written information as well as the form for the Declaration of consent of the participants are attached to this application.

In the course of the study, due to the aspects mentioned in point 6. and 7.2.1, no serious adverse effects are expected. In the event of serious events, both the clinic management and the ethics Committee will be informed immediately.

8.2. Participants with no ability to consent

The study includes only patients who can decide on their own to participate in the study.

8.3. Research on minors

Not applicable, since only persons with an age of at least 18 years are included.

9. Data protection

The highest priority is given to the data protection of the participants:

Only the most important personal data are collected (first name, name, date of birth, age, sex).

All data collected will be treated confidentially. They are stored or saved without a name and without using the date of birth under a code number (pseudonymized). Material containing information about individual persons is locked and kept separate from the encoded data. The medical confidentiality and the data protection regulations are respected. The evaluation is carried out solely by employees of the hospital, all of whom are subject to confidentiality. No individualized data will be passed on to third parties. Participants will be informed about this procedure.

The mentioned points are explained in the patient information and in particular the data protection declaration of consent.

10. Insurance

An insurance contract is not planned because this study project does not provide for a procedure with not very low risks for the participants of the study. Study-related trips of the participants to the study are not insured. It is a therapy offer.

11. Financing

Secondary costs are not to be expected.

Dr. Monika Empl is training to be a Introvision consultant in order to be able to teach Introvision for the participants of the study. A separate remuneration of the investigating physician does not take place, however, if a sponsor is found, an allowance (also for travel costs) for the Introvision consultants and the investigator is provided. As a sponsor, the Klaus-Grawe-Foundation, Zurich, is requested. A patient remuneration is not foreseen.

The costs of the allowance expenditure for the ethics committee are taken over.

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List of References

1. Wagner, AC. Gelassenheit durch Auflösung innerer Konflikte. *Mentale Selbstregulation und Introvision*. 2. Edition, Kohlhammer Verlag, 2011.
2. Pape N. *Introvision als Entspannungsverfahren – Auflösung von chronischen Nackenverspannungen durch Konstatierendes Aufmerksames Wahrnehmen und Introvision*. In: *Gruppendynamik und Organisationsberatung*, 2008; 2:184-198.
3. Buth B. *Die Anwendung von Introvision zur Verringerung der Belastung durch Tinnitus und Verbesserung der Hörfähigkeit*. *Gruppendynamik und Organisationsberatung*. 2008; 2:212-224.
4. Pereira Guedes N. *Dauerhafte Auflösung chronischer Nackenverspannungen durch Introvision: Eine empirische Untersuchung einer pädagogisch-psychologischen Intervention zur mentalen Selbstregulation*. 2011; Dissertation; Universität Hamburg.
5. Benthien O. *Der Einsatz von Introvision als Stressinterventionsverfahren im Leistungssegelsport. Eine theoretische und empirische Untersuchung*. 2011; Dissertation; Universität Hamburg.
6. Evers S. *Relevance of headache for population medicine. Health care, costs, working loss*. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2014; 57:946-51.
7. Fritzsche G, Kröner-Herwig B, Kropp P, Niederberger U, Haag G. *Psychological therapy of migraine: systematic review*. *Schmerz*. 2013; 27:263-74.