1. General information

Project title

Transcutaneous Vagus-Nerve Stimulation for the Treatment of Adolescent Depression – An Experimental Proof-of-Concept

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Sponsors

none

Date/Version of the study plan

May, 18th 2016; Version 1.0

Signatures of principal investigators

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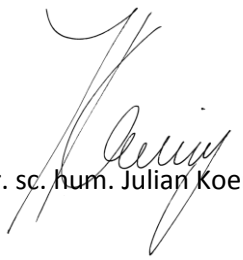

Dr. sc. hum. Julian Koenig

2. Summary

Depression is the 2nd leading cause of disability worldwide. About 2.8% of children under the age of 13, and 5.6% of adolescents (13-18 years) fulfill diagnostic criteria for depression. Depression among adolescents is a major risk factor for suicide, which is one of the leading causes of death in this age group. Most importantly, about 40% of children and adolescents with depression do not benefit from the treatment options available (termed: treatment resistant depression). Vagal activity – a psychophysiological marker of emotion regulation – is decreased in adolescents with depression, and provides a potential physiological pathomechanism underlying depressive symptomatology. Vagus nerve stimulation (VNS) is effective in the treatment of adults with treatment resistant depression, leading to improved mood and overall wellbeing. Transcutaneous VNS (tVNS) is a new technology, allowing for the non-invasive VNS that is considered safe for the use in children and adolescents. However, proof of concept studies, showing that tVNS alters vagal activity and depressive symptoms by improving mood and emotion regulation in adolescents with depression are missing. Filling this gap is crucial, to offer a treatment option for depressed adolescents. The purpose of the present project is to investigate the effects of tVNS on neuropsychological proxies of depression in a sample of 30 adolescents with major depression. Adolescents will perform neuropsychological tasks addressing difficulties in emotion regulation and emotion recognition while receiving tVNS or sham stimulation. Results are promising with respect to the further development of tVNS as alternative treatment option for treatment resistant depression in youth.

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4. Introduction

4.1. Depression in adolescents

Depression is the 2nd leading cause of disability worldwide, with at least 20% of people in developed countries experiencing the disorder at some point in their lives (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). About 2.8% of children under the age of 13, and 5.6% of adolescents between the 13-18 years of age fulfill diagnostic criteria for depression, with overall prevalence rates among adolescent girls being slightly higher than among boys(Costello, Foley, & Angold, 2006) Depression among children and adolescents (C&A) is a major risk factor for suicide, which is of the leading causes of death in this age group (Windfuhr et al., 2008). While psychotherapy such as *Cognitive Behavioral Therapy* (CBT) (Reinecke, Ryan, & DuBois, 1998) may be beneficial for C&A with depression not all patients benefit from the existing psychotherapeutic treatments available. *Selective Serotonin Reuptake Inhibitors* (SSRI) such as *Fluoxetine* are effective in the reduction of depressive symptoms in C&A but there is evidence of an increased risk of suicide related outcomes in those treated with SSRIs (Hetrick, Merry, McKenzie, Sindahl, & Proctor, 2007). Tricyclic antidepressants that are used in adults are not superior to placebo for the treatment of depression in C&A (Ambrosini, 2000). Overall, only 60% of C&A with depression respond to initial treatment with pharmacotherapy or psychotherapy, while about 40% show treatment resistant depression (TRD) (Bridge et al., 2007; Weisz, McCarty, & Valeri, 2006). The risks of polypharmacy and iatrogenic harm are high in C&A with TRD, calling for a non-pharmacological treatment option to alter depressive symptoms if psychotherapy and pharmacotherapy show ineffective.

4.2. Vagal activity in adolescents with depression

Among adults, depression is associated with reduced vagal activity, indexed by heart rate variability (HRV), and these reductions are inversely correlated with depression severity (Kemp et al., 2010). Recently we were able to show, that adolescents with depression also show decreased resting state vagal activity indexed by HRV (Koenig, Kemp, Beauchaine, Thayer, & Kaess, 2016). HRV is an index of parasympathetic nervous system function and chronic reductions reflect poor physiological, emotional, cognitive, and behavioral regulation and are associated with numerous risk factors as well as self-rated heath (Alvares et al., 2013a; Beauchaine & Thayer, 2015; Jarczok et al., 2015; Thayer & Lane, 2000; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012; Thayer, Hansen, Saus-Rose, & Johnsen, 2009; Thayer & Lane, 2009). Among other things, a consequence of impairment in the vagus nerve reflected by HRV – and the high-frequency [HF]-HRV component in particular – is a poorly functioning anti-inflammatory reflex (Pavlov & Tracey, 2012), increasing risk for physical ill-health (see Kemp & Quintana, 2013 for a review). Time- and frequency-domain measures of HF-HRV reflecting fast parasympathetic modulation of autonomic control of the heart, provide a feasible and readily available index of vagal activity. Both time- and frequency-domain measures of HF-HRV are consistently used in the literature as an index of vagal activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). HF-HRV may be considered a peripheral index of individual differences in perception of emotional stimuli (Park & Thayer, 2014; Park, Van Bavel, Vasey, & Thayer, 2013) that predicts affective instability in daily life (Koval et al., 2013). As several authors have noted, HF-HRV is correlated with difficulties in emotion regulation among child, adolescent, and adult samples (see e.g. Beauchaine, 2015; Berna, Ott, & Nandrino, 2014; Williams et al., 2015).Resting state vagal activity is a biomarker of clinical relevance with respect to diagnosis, monitoring, and treatment of depressed patients. In fact, reduced resting state HF-HRV is both a correlate of depression among adults (e.g. Kemp et al., 2010), and a marker of treatment response (Chambers & Allen, 2002; Chien, Chung, Yeh, & Lee, 2015) such that decreases in depressive symptoms are associated with increases in HRV.

4.3. Vagus-Nerve Stimulation

Treatment options designed to increase vagal activity might lead to symptom improvement in depressed children and adolescents. Vagus-nerve stimulation [VNS] was originally developed for the treatment of epilepsy (Ben-Menachem, 2002) and it is now a promising treatment option for adult patients with chronic or recurrent, treatment-resistant depression (Nahas et al., 2005; Rush et al., 2005). Invasive VNS is reported to be a safe and feasible procedure, although its concrete mechanism of action are not yet well evaluated for the treatment of affective disorders (Daban, Martinez-Aran, Cruz, & Vieta, 2008). Recent technological developments allow for noninvasive transcutaneous tVNS, that is considered a safe and well-tolerated method and alternative treatment option in epilepsy (Stefan et al., 2012), including in pediatric patients (He et al., 2013). Recently it has been shown, that tVNS modulates the functional connectivity of the default mode network in MDD (Fang et al., 2015) and may lead to increases in well-being by decreasing activity in limbic brain areas, including the amygdala (Kraus et al., 2007). Preliminary case studies on tVNS in the treatment of MDD are promising (Trevizol et al., 2015) and clinical trials in adults are ongoing (Rong et al., 2012). Animal studies suggest that tVNS may act as an antidepressant by triggering melatonin secretion (Li et al., 2014) and by leading to increases in HF-HRV (Clancy et al., 2014).

4.4. Research Gap and Main Objectives

Proof of concept studies showing that tVNS alters vagal activity and depressive symptoms by improving mood and emotion regulation in C&A with depression are missing. Filling this gap is crucial, to offer a treatment option for depressed C&A not responding to existing interventions and thereby reducing the risk of suicide in our youth with treatment resistant depression. The aim of the present project is to test whether tVNS can alter core characteristic proxies (namely negative mood and difficulties in emotion regulation) of depressive symptomatology in C&A with depression. The specific hypothesis to be tested is that C&A with depression show better emotion regulation and improved mood while receiving tVNS compared to sham-tVNS. If empirically proven by the proposed project, the findings have important implications for future research and clinical practice. Alternative treatment approaches for treatment resistant depression in C&A are desperately needed and tVNS provides a unique opportunity to address a mental health problem of crucial prevalence.

5. Procedures

5.1. General description

An experimental placebo controlled (sham versus tVNS) design is used. Adolescents (14-17 years) perform neuropsychological tasks and provide self-reports of current mood and distress while receiving tVNS or sham (cross-randomized). 30 adolescents fulfilling DSM-5 diagnostic criteria for major depression will be enrolled. Adolescents undergo routine diagnostic procedures including assessments of basic sociodemographic characteristics, depressive symptoms and comorbid psychopathology. After physical examination adolescents with severe somatic symptoms will be excluded. Heart rate variability as index of vagal activity will be recorded continuously using electrocardiogram throughout the procedure. Similar, functional near infrared spectroscopy (fNIRS) will monitor oxygenation of the prefrontal cortex as index of cognitive load under task conditions. Primary outcomes are the performance on the Emotional Go/No-Go (emotion regulation) and Face-Recognition (emotion processing) task and changes in self-reports of mood and distress. The Emotional Go/No-Go task is a computerized task presenting neutral faces or faces of a distinct emotional valence simultaneously with a command of action (“press button”). C&A are trained to inhibit a response (i.e., not to press the button) on certain cue words. Successful inhibition on the task is a well-established measure of emotion regulation, and by evidence impaired in patients with

depression. The Face-Recognition task measures the ability to correctly classify emotional expression in the face of others. Depressed patients show difficulties in emotion recognition and tend to classify positive emotions (i.e., joy or happiness) as negative (i.e., fear and anger). Early changes in emotion processing have been shown to predict treatment outcome in clinical studies on pharmacotherapy for depression. Outcomes on both tasks are measures by correct responses (i.e., action or classification) and response time (i.e., in milliseconds). Self-report on positive and negative mood as well as sate-dependent distress will be obtained using visual analogue scales.

5.2. Effects

The whole test battery consists of psychometrical, diagnostically, or neurobiological inventories that have been officially approved. Part of the clinical interviews and the questionnaires are used during routine diagnostics in our Department. The study could help to get important insights into the effect of tVNS on depressive symptoms, which in turn might help to improve interventreatmenttion programs for depressed adolescents.

5.3. Undesirable effects

tVNS is a non-invasive technique that has previously been used in C&A with epilepsy. The device that we will use is CE approved and intended for the treatment of depression. Previous consultation with the institutional review board revealed no ethical concerns. However, we will take precautions with respect to the presence of medical personal during tVNS stimulation to ensure the health and safety of our patients. Undesirable effects are not expected.

6. Study design

Study Design: The study utilizes a within-subject cross-over, placebo-.controlled (sham vs. tVNS) design. The study protocol comprises two appointments on separate days: T1 (~120 min) is dedicated to the extensive diagnostic assessment psychiatric characterization of the sample. At T2 (~120 min) the actual experiment is conducted. The design is illustrated in *Figure 1*.

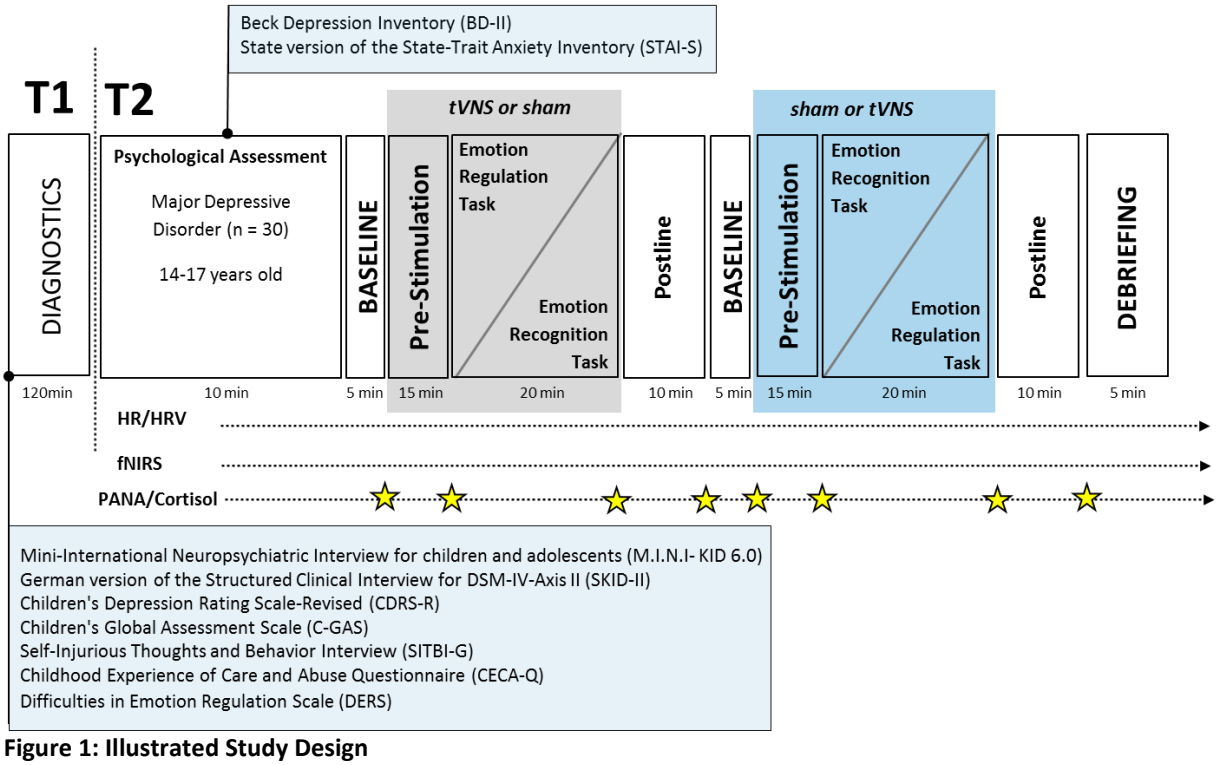


Figure 1: Illustrated Study Design

Population: A groups of adolescents (14-17 years of age) n=30 will be enrolled. All adolescents fulfill diagnostic criteria for major depression according to the Diagnostics and Statistical Manual for Mental Disorders 5th edition(American Psychiatric Aociation, 2013) as determined by a structured clinical interview conducted by experienced psychologists.

Interventions: At T2 adolescents will receive tVNS and sham (wearing the tVNS device with no effective stimulation) in a cross-randomized order for a total of 30 minutes each (baseline, tasks, postline) while repeatedly completing neuropsychological tasks and providing self-reports. The tVNS device to be used (VITOS, Cerbomed GmbH) consist of an ear plug, applying electrical stimulation of the auricular branch of the vagus nerve distributed to the skin of the ear. Similar, sham will be applied to the ear, set up not to stimulate the vagus nerve, as described elsewhere. The VITOS tVNS stimulator is manufactured by CerboTec in Erlangen, Germany. The device is CE approved for the indication of treating depressive symptoms. Technical documentation for the device and the CE approval are provided as supplementary material.

7. Inclusion criteria

- therapy in our clinic
- major depressive disorder
- aged 14 to 17 years
- informed consent of study participants and of a parent or a person having parental authority

8. Exclusion criteria

- poor knowledge of the German language
- intake of medicines containing glucocorticoids
- pregnancy
- primary neurological or endocrinological disease
- acute psychotic symptoms
- acute suicidality
- any cardiovascular disease

9. Randomization procedures

A cross-randomized within-subject trial will be conducted. Patients will receive both, short-term tVNS or sham-tVNS in a randomized order within one experimental session.

10. Study procedure

10.1. Recruitment strategy

Depressed patients will be recruited through our Clinic for Child and Adolescent Psychiatry, by established procedures. In order to ensure enrollment and retention of the sample size, 45 patients will be recruited, of which we expect to enroll 36-40. Pending on the drop-out between T1 and T2 we expect a per-protocol sample of at least 30 adolescents. With respect to the timeline of the study, previous experiences in recruiting depressed adolescents, and the clinical presentation of depressed

adolescents (that are of the largest groups that present themselves to our clinic) the recruitment of 45 adolescents is feasible within 18 months.

10.2. Written Informed Consent

Patients receiving therapy at our clinic will be informed about the content and procedures of the study. In case, they are interested in participation and are meeting the criteria for study inclusion, we will provide written information to patients and their parents (or alternatively persons having parental authority). All patients will receive detailed information about the scientific contributions, the study procedure and potential risks. Patients and their legal guardians are asked to provide written informed consent prior to inclusion in the trial.

10.3. Psychological Assessments

At T1 sociodemographic information is taken and a basic physical examination is conducted (i.e., weight, height). Psychiatric diagnoses will be obtained using the *Mini-International Neuropsychiatric Interview for C&A*.(Sheehan et al., 2010) In addition, the *Structured Clinical Interview for DSM-IV-Axis II* will be used to assess symptoms of personality disorders.(Fydrich, Renneberg, Schmitz, & Wittchen, 1997) Assessments further include the *Children's Depression Rating Scale* to assess the severity of depressive symptoms by a trained clinician.(Mayes, Bernstein, Haley, Kennard, & Emslie, 2010). The *Self-Injurious Thoughts and Behavior Interview* (Fischer et al., 2014) will be used for the assessment of suicidal and self-injurious behavior.

The *Childhood Experience of Care and Abuse Questionnaire*.(Kaess et al., 2011) will be used to obtain information on childhood trauma, and the *Children's Global Assessment Scale* will be used to rate the psychosocial functioning of adolescents.(Shaffer et al., 1983) Further, patients are asked to complete the *Difficulties in Emotion Regulation Scale* (Kaufman et al., 2015), to assess their everyday difficulties in coping with emotions.

At the day of the experiment (T2), adolescents first provide self-reports on their current depressive symptoms on the *Beck Depression Inventory*(Beck, Steer, Ball, & Ranieri, 1996) and complete the *State Trait Anxiety Inventory.*(Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). While completing neuropsychological tasks, adolescents provide self-repots on mood and distress repeatedly (see *Figure 1*) using visual analogue scales and the *Positive and Negative Affect Schedule* (PANAS) (Crawford & Henry, 2004).

10.3. Neurobiological Measurements

Electrocardiogram (ECG) to quantify vagal activity by measures of HF-HRV and functional near infrared spectroscopy (fNIRS) to quantify oxygenation of the prefrontal cortex as index of cognitive load are measures throughout the experimental procedures at T2. Both measures are non-invasive in nature. Patients will wear a chest-belt and sensor for the ECG recording (ECG Move3 Sensor, Movisens, Karlsruhe) and a headband with the respective sensor (Octamon, Artinis Medical Systems, Elst, Netherlands). The fNIRS uses near-ifrared light to measure oxygenation of the prefrontal cortex. In line with the assessment of mood and distress (PANAS), participants are asked to provide saliva samples for the assessment of cortisol. Saliva samples will be collected by participants at eight time points throughout the procedures using cotton roles and collection tube (Salivette, Sarstedt). Consequently, samples will be frozen at −20 degrees Celsius. Salivary cortisol will be analyzed at the Steroid Laboratory of the Department of Pharmacology, University of Heidelberg, by a specific in-house radioimmunoassay (RIA) using tritiated steroid (Amersham Biosciences, Freiburg, Germany) and antibodies, raised and characterized in the steroid laboratory.

10.4. Neuropsychological Tasks

Adolescents repeat neuropsychological task to assess emotion processing and emotion regulation under tVNS and sham. Emotion recognition is measured by the participants' capability to correctly recognize key facial expressions using a well evaluated computerized task. Neutral facial stimuli will be displayed that slowly morph (1% pre 500 ms) towards a target emotion in facial expression (happy, sadness, anger, disgust, fear and surprise). Patients are asked to indicate the expressed emotion by pressing a button on the keyboard as fast and as accurate as possible. Time and accuracy are taken as dependent measures. The task comprises sets of stimuli that are presented cross-randomized (tVNS *vs*. sham). Reaction time in milliseconds and correct classifications are measured as outcome.

Changes in emotion regulation are assessed using the emotional *Go/No-Go* paradigm. The paradigm involves a continuously presented series of faces of certain emotional valences (e.g., happy, angry) composed of frequent "*Go*" cues (i.e. angry faces) to which patients respond as rapidly as possible (pressing key on keyboard) and infrequent "*No-Go*" (i.e., happy faces) cues to which patients do not respond and inhibit their response. The frequency of *Go* cues (≥ 75%) creates a prepotent tendency to respond that in the following must be inhibited for *No-Go* cues, thereby providing a measure of the ability to inhibit a prepotent emotional response. Again, reaction time in milliseconds and correct performance are measured as outcome.

11. Adjuvant therapy

All patients are attending different therapeutic options within our clinic.

12. Safety laboratory

Not applicable

13. Criteria for study termination

The termination of study participation can happen at any time if adolescents or alternatively their parents or persons having parental authority are withdrawing their written consent.

14. Statistical analyses

Power Calculation: Data from previous research comparing the within-subject effects of tVNS vs. sham on neuropsychological tasks in healthy subjects (Steenbergen et al., 2015) were used for power calculation on intervention effects. Given an effect size of d=1.154, analysis assuming a set α=0.05 for paired test are capable to detect intervention effects at sample size of 8 down to a β=0.10. Correcting for multiple testing in a one-factorial ANOVA (condition) and post-hoc contrasts a per-protocol sample size of n=30 is sufficient to detect significant main effects. Effects of tVNS versus sham on vagal activity, and within-subject effects on self-reported mood and distress, are described at larger effect sizes, thus the sample size is sufficiently powered to also detect significant main effects on the physiological measures and self-reports taken. fNIRS is considered an exploratory indicator of cognitive load and not assumed a main outcome.

Statistical Analysis: As indicated in the characteristics of power calculation, a full-factorial mixed model including fixed (participant) and random (tVNS vs. sham) factors will be calculated to address

intervention effects on the main outcomes of neuropsychological task performance (correct classifications and response time in face recognition and emotional Go/No-Go), physiology (HF-HRV and fNIRS), and self-reports (mood and distress). Mixed models are followed by planned contrasts. Secondary analysis will utilize regression models to predict task performance by baseline physiology and correlation analysis to explore the association of physiological changes under tVNS, task performance and self-reports. A department based biostatistician (Mr. Peter Parzer) consults the project. Confounders: A host of potential confounders will measured and controlled for in the analysis. Beyond the sociodemographic (age, gender, weight and height) and psychiatric confounds mentioned (history of trauma, personality disorder, comorbidity). Predicted marginal means adjusting for the aforementioned factors will be derived from mixed models to control for these confounders.

15. Ethical aspects

The study will be conducted in accordance to the declaration of Helsinki and the rules for physicians of the medical association ("Landesärztekammer") of Baden-Württemberg in their currently valid version. Study participation is voluntary. The consent can be withdrawn at any time without stating the reason and without any individual disadvantage for subsequent medical care. Study participants and their parents or alternatively persons with parental authority will be informed in written form about the procedures and potential undesirable effects or risks of our study. Their approval will be documented via their signature on the informed consent. In case of study withdrawal, previously collected data will be destroyed if participants do not give their consent for the analysis of those data. The tVNS device used is CE certified and intended for the treatment of depression.

16. Legal aspects

The study program will be submitted to the ethics commission of the medical faculty of the University of Heidelberg for consulting of professional conduct prior to the start of our study. We will not include any patients before receiving the written vote of the ethics commission. The names of participants and all confidential information are subject to medical confidentiality and to the requirements of the Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG). The data will be stored and processed in a pseudonymized manner. No third parties will gain insights into the original data.

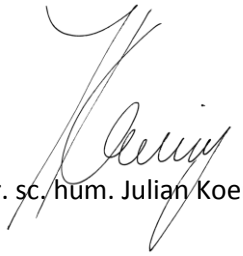
17. Appendices

Information sheets, technical documentation of the tVNS device, documents for informed consent, and all questionnaires are provided with the respective version number and date in the appendices.

18. Signatures

Heidelberg, May 18th 2016

Dr. med. M. Kaess



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