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DELirium treatment with Transcranial Electrical Stimulation (DELTES): study protocol for a multicentre, randomised, double-blind, sham-controlled trial

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ABSTRACT

Introduction: Delirium, a clinical manifestation of acute encephalopathy, is associated with extended hospitalisation, long-term cognitive dysfunction, increased mortality, and high health care costs. Despite intensive research, there is still no targeted treatment. Delirium is characterised by electroencephalography (EEG) slowing, increased relative delta power and decreased functional connectivity. Recent studies suggest that transcranial alternating current stimulation (tACS) can entrain EEG activity, strengthen connectivity, and improve cognitive functioning. Hence, tACS offers a potential treatment for augmenting EEG activity and reducing the duration of delirium. This study aims to evaluate the feasibility and assess the efficacy of tACS in reducing relative delta power.

Methods and analysis: DELTES is a randomised, double-blind, sham-controlled trial conducted across three medical centres in the Netherlands. The study comprises two phases: a pilot phase (n=30) and a main study phase (n=128). Participants are patients aged 50 years and older who are diagnosed with delirium (DSM-5-TR criteria) that persists despite treatment of underlying causes. During the pilot phase, participants will be randomised (1:1) to receive either standardised (10 Hz) tACS or sham tACS. In the main study phase, participants will be randomised to standardised tACS, sham tACS, or personalised tACS, in which tACS settings are tailored to the participant. All participants will undergo daily 30 minutes of (sham) stimulation for up to 14 days or until delirium resolution or hospital discharge. Sixty-four-channel resting-state EEG will be recorded pre- and post the first tACS session, and following the final tACS session. Daily delirium assessments will be acquired using the Intensive Care Delirium Screening Checklist (ICDSC) and Delirium Observation Screening Scale (DOSS). The pilot phase will assess the percentage of completed tACS sessions and increased care requirements post-tACS. The primary outcome variable is change in relative delta EEG power. Secondary outcomes include (1) delirium duration and severity, (2) quantitative EEG measurements, (3) length of hospital stay, (4) cognitive functioning at three months post-tACS, and (5) tACS treatment burden. Study recruitment started in April 2024 and is ongoing.

Ethics and dissemination: The study has been approved by the Medical Ethics Committee (MREC) of the Utrecht University Medical Center and the Institutional Review Boards of all participating centres. Trial results will be disseminated via peer-reviewed publications and conference presentations.

Trial registration: ClinicalTrials.gov (NCT06285721). Registered on 19-02-2024.

Strengths and limitations of this study

- This study introduces an innovative potential treatment for delirium, which is hypothesised to reverse and treat altered brain activity during acute encephalopathy presenting as delirium.
- To our knowledge, this is the first randomised controlled trial to investigate transcranial alternating current stimulation (tACS) as treatment for delirium.
- In addition to evaluating the effectiveness of tACS, the study also considers its feasibility and burden as delirium treatment.
- Recognising the knowledge gap in optimal stimulation settings for delirium, this study aims to incorporate a personalised treatment arm that tailors tACS settings to each individual participant.
- The study's applicability to hyperactive delirium may be limited due to the requirement for patients to complete EEG assessments.

INTRODUCTION:

Delirium, a neuropsychiatric syndrome characterised by an acute disturbance in consciousness and cognition precipitated by an medical condition such as infection or surgery, affects approximately 23% of medical inpatients.[1,2] It is associated with extended hospitalisation, long-term cognitive dysfunction, increased mortality, and increased health care costs.[3–8] There is no specific treatment for delirium itself. Current management strategies primarily target precipitating factors and employ (non-)pharmacological interventions to alleviate symptoms.[1,9] As duration of delirium is independently associated with worsened long-term cognitive outcomes and dementia, interventions to treat delirium itself are needed.[4,10,11]

Delirium is one of the clinical manifestations of acute encephalopathy, a rapidly developing pathobiological process in the brain,[12] measurable by electroencephalography (EEG). EEG power spectral analysis in patients with acute encephalopathy presenting as delirium consistently shows increased power in delta and theta bands, primarily in frontal regions, and reduced power in the alpha band, predominantly in occipital and parietal regions.[13–19] Of these changes, reduced relative delta power (0.5 - 4 Hz) is the most robust feature and can be used to classify the presence of delirium based on EEG compared to non-delirious control patients.[20,21] This shift to slow wave activity correlates with delirium severity, strengthening the evidence for a relation between these phenomena.[19] Furthermore, delirium is associated with decreased functional brain connectivity and reduced network efficiency in the alpha frequency band.[16,17] Studies using functional magnetic resonance imaging have demonstrated decreased integration and efficiency of the default mode network (DMN) in patients with postoperative delirium.[22,23] Another study showed that network alterations persist after three months and correlate with cognitive impairment, indicating an association between connectivity changes and cognitive outcomes.[24]

Recent studies in healthy individuals have demonstrated the potential of transcranial alternating current stimulation (tACS) in modulating brain activity by entrainment of specific cortical rhythms based on the applied stimulation frequency.[25–27] The administration of tACS is suggested to phase-lock large populations of neurons in the superficial layers of the cerebral cortex, inducing neural synchronisation in the corresponding frequency, and changing brain connectivity.[28,29] Studies on healthy individuals have revealed that tACS applied in the alpha frequency range can augment alpha activity and functional brain connectivity,[25,30–33] both affected during delirium.[34] Furthermore, a meta-

analysis has indicated a clear beneficial effect of tACS on cognition in other populations, including improvements in attention and working memory, [35] which are cognitive domains also affected during delirium. [1] Interestingly, a recent study with healthy volunteers showed that alpha-tACS not only augments alpha activity but also strengthens connectivity within the DMN, [25] the primary network disturbed during delirium.[22,23] Additionally, oscillatory entrainment can have cross-frequency effects, [30,36] meaning that tACS applied within the alpha frequency range can lead to a decrease in relative delta power. Taken together, tACS might be able to reduce delta activity, reinforce alpha activity and connectivity in brain regions that show altered connectivity during delirium, [22,23] potentially offering therapeutic benefits.

When applying tACS as a potential treatment for delirium, the most straightforward approach is to apply tACS in the alpha frequency range, targeting both reduced alpha power and functional connectivity seen in delirium.[15–18] However, numerous approaches in terms of stimulation location and frequency are possible, which might be equally or more effective in treating delirium than alpha-tACS. Incorporating functional brain connectivity changes of individual patients into personalised treatment could improve treatment effectiveness, reduce adverse effects, decrease the need for trial and error in clinical trials, and enhance our understanding of the mechanisms underlying treatment effects.[37] The use of computational models may allow one to infer how modifications of neuronal properties might influence emergent neuronal activity and treatment response.[38] A promising type of computational model is the neural mass model, which models brain activity of large populations of neurons.[39] Using a network of coupled neural masses, neuronal activity similar to an encephalopathic EEG has been simulated. [40] Building on this, this study will apply neural mass modelling of individual functional connectivity changes in a virtual trial to optimise treatment settings.

In the current trial, we will evaluate whether tACS normalises brain activity, specifically relative delta power, in delirium. To date, no RCTs investigated tACS as treatment for delirium, highlighting significant gaps in our understanding of the feasibility, effectiveness and the most effective application strategies. Therefore, the trial will begin with a pilot phase aimed to assess feasibility. Upon successful completion of the pilot phase, the main study phase will commence with three study arms to assess the efficacy of tACS in reducing relative delta power: a standardised treatment arm, a sham control arm and a personalised treatment arm based on a computational model and virtual trial. We hypothesise that both standardised and personalised tACS will decrease relative delta power

compared to sham tACS in delirium patients. By adopting this two-step approach, this study aim to evaluate the feasibility as well as the effectiveness of tACS in patients with delirium.

METHODS AND ANALYSIS

Study objectives

For the pilot phase, the primary objective is to evaluate the safety and tolerability of tACS in patients with delirium. The main study phase aims to determine the efficacy of a single session of standardised or personalised tACS in reducing EEG relative delta power in patients with delirium. Secondary objectives include assessment of the impact of daily standardised or personalised tACS compared to sham on the duration and/or severity of delirium, the length of hospital stay, and cognitive functioning three months after the initial tACS session.

Study design and setting

This study is a double-blind, randomised controlled trial conducted across three medical centres in the Netherlands: the University Medical Center (UMC) Utrecht, Radboud UMC and HagaZiekenhuis. To assess safety and feasibility of tACS in delirious patients, the study will start with a pilot phase in which 30 patients will be randomised in a 1:1 ratio to receive daily either standardised active tACS or sham treatment for a maximum of 14 days, or until resolution of delirium or hospital discharge.

Upon completion of the pilot phase, the main study phase will begin, introducing the personalised treatment arm. Criteria for continuing to the main study phase are defined under outcomes. All patients from the pilot phase will be included in the main study analyses. Randomisation weights will be recalculated, and participants will be allocated in an overall 1:1:1 ratio to receive either standardised tACS, personalised tACS, or sham treatment (i.e., combining personalised sham and standardised sham tACS into one arm). The baseline visit will include delirium assessment using the Delirium Interview [41], administered by a trained researcher, and reviewed by an expert delirium panel. Furthermore, information will be collected from the electronic patient record and the clinical frailty scale (CFS) [42] will be evaluated. After these assessments, the first treatment session starts which includes a 64-channel EEG measurement before and after the first tACS or sham treatment. Also, a questionnaire on sensation to assess possible adverse events of tACS, a questionnaire on feasibility and questionnaire on blinding and subjective treatment experiences (Appendix 1) will be administered. Following this, daily tACS or sham treatment visits and delirium assessments will take place for a maximum of 14 days, or until resolution of delirium or hospital discharge, whichever comes first. The treatment phase will end with a close out visit including a follow-up 64-channel EEG and

administration of the questionnaires on sensation, blinding and subjective treatment experiences. A brief cognitive assessment using the Telephone Interview for Cognitive status, modified version (TICS-M) [43,44] is planned at three months after the first tACS session. The study design is illustrated in Figure 1, and the study schedule is presented in Table 1.

Figure 1. Study flowchart. tACS = transcranial alternating current stimulation; EEG = electroencephalography; V = visit, T= treatment.

Sample size and statistical power

The sample size calculation is based on data obtained from a previous study that examined EEG findings in both delirious and non-delirious patients.[45] In this study, patients with delirium showed a median relative delta power of 0.59 (interquartile range (IQR) 0.47-0.71), while those without delirium had a median of 0.20 (IQR 0.17-0.26), resulting in an effect size of 0.39 (0.20 – 0.59). This study excluded patients in whom the diagnosis delirium was not certain, which may have inflated the effect size. It is therefore anticipated that both standardised and personalised tACS will lead to a more modest decrease of 0.15 in relative delta EEG power post-stimulation compared to pre-stimulation measurements. Based on these assumptions, a sample size of 159 participants (i.e., 53 per group) was estimated using G*Power 3.1. This estimation considered an effect size of 0.15 with a standard deviation of 0.3, an alpha of 0.025 (adjusted for multiple testing using Bonferroni correction), and 80% statistical power. As the primary outcome assessment occurs right after the first treatment, no attrition is expected.

Study population

In total, 159 patients aged 50 years or older with a diagnosis of delirium will be included in the study.

Inclusion criteria for eligibility

In order to be eligible to participate in this study, a participant must meet all of the following inclusion criteria:

- Age over 50 years.
- Diagnosis of delirium.
- Richmond Agitation and Sedation Scale (RASS) [46] score of -2 to +2.

- Delirium duration of at least two days prior to study inclusion, based on delirium assessments and/or descriptions in the medical and/or nursing files.
- Causes underlying delirium are being treated adequately, as assessed by the treating physician and a panel of delirium experts (i.e., psychiatrist, geriatrician and intensivist).

Exclusion criteria for eligibility

A potential participant who meets one or more of the following criteria will be excluded from participation in this study:

- Inability to conduct valid delirium screening assessment (e.g. deaf, blind) or inability to speak Dutch or English.
- A moribund state.
- Alcohol/substance abuse withdrawal or stroke as the presumed cause of delirium.
- Diagnosis of dementia, based on medical record review and/or a score of ≥4.5 on the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[47].
- Brain injury of any type (e.g. traumatic, vascular, post anoxic) in the previous six weeks.
- One or more contra-indications for tACS:
  - Large or ferromagnetic metal parts in the head (except for a dental wire).
  - Implanted cardiac pacemaker or neurostimulator.
  - Skin disease or inflammation at the stimulation sites.
  - History of epilepsy.

Inclusion criteria for randomisation

- All inclusion criteria are met.
- Diagnosis of delirium is confirmed using the Delirium Interview [41] and consultation with a delirium expert who is part of the research team (psychiatrist, geriatrician and/or intensivist).
- Written informed consent obtained from legal representative.

Patient withdrawal

If a patient and/or legal representative is wants to withdraw from the study, they can do so without any consequences. We will adhere to the definitions and guidelines stipulated in the code of conduct relating to the expression of objection by incapacitated (psycho)geriatric patients in the context of the WMO (2002). The clinician or investigator can decide to withdraw a subject from the study for urgent medical reasons. There are no expected negative effects of prematurely ending the stimulation sequence.

Procedures (time needed)	Baseline visit (V1)	First treatment visit (T1)	Additional treatment visits (T2 up to T14)	Post-treatment visit (V2)	Follow-up visit (V3)
Medical history[a]	X				
Physical health[a]	X				X
Current medication use[a]	X	X	X	X	X
Clinical Frailty Scale[a]	X				
Sensation questionnaire (5 min)		X		X	
Blinding and subjective treatment experience (1 min)		X		X	
Feasibility questionnaire (5 min)		X			
Delirium Interview (10 min)	X				
ICDSC (10 min)	X	X	X	X	
DOSS (5 min)[b]	X	X	X	X	
TICS-M (10 min)					X
EEG (40 min)	X[c]	X		X	
tACS (30 min)		X	X		
Estimated total duration	25 or 60 min[c]	95 min	45 min	65 min	15 min

Table 1. Overview study procedures. ICDSC = Intensive Care Delirium Screening Checklist; DOSS = Delirium Observation Screening Scale; TICS-M = Telephone Interview for Cognitive status, modified version; EEG = Electroencephalogram, tACS = transcranial altering current stimulation.

[a] = this information will be recorded as part of standard clinical care, and missing information will be requested via family and will therefore not require additional time.

[b] = only non-Intensive Care Unit (ICU) patients will be assessed using the DOSS

[c] = only the group randomised to personalised tACS will receive an EEG during the baseline visit.

Informed consent, randomisation and blinding

For surgical patients, a flyer is provided during the pre-operative screening to inform patients and their legal representatives about the study, enabling them to familiarise themselves with this study in advance and consider participation in the event of delirium occurrence. In non-surgical patients, this flyer is provided to the wards with the request to hand this to newly admitted patients. Consultants, including psychiatrists, geriatricians and neurologists, and ward physicians are asked to screen for potential participants. Upon identification of patients eligible to participate in the trial, consultants and ward physicians inform the research team. The research team will inform the patient and their legal representatives about the study. If the patient and legal representative are possibly willing to participate, the investigator provides the information letter and provides them at least one day to consider study participation. If a patient is eligible for study participation, initial informed consent will be obtained from a legal representative, as the patient may be unable to provide consent when delirious. Legal representation is identified using a hierarchical model consistent with local and national laws and regulations. Once patients regain capacity to provide informed consent, they will be asked to provide written informed consent themselves. At any time, the patient or their legal representatives can refuse or withdraw consent for the study without providing a reason and without impacting the treatment provided.

Delirious patients who meet all inclusion criteria but none of the exclusion criteria for eligibility and randomisation will be randomised to one of the study arms. Randomisation will be conducted electronically via the Castor Electronic Data Capture (EDC) study management system (Castor, Ciwit B.V., Amsterdam, the Netherlands), using a validated block randomisation model, stratified by study centre. In the pilot phase, standardised active tACS and sham carry equal weight (1:1). Patients will be randomised with block sizes of 2 and 4. In the main study phase, four groups will be created in Castor EDC (standardised active, personalised active, standardised sham, personalised sham) with different weights, depending on the number of participants who have been randomised to the active and standardised sham groups during the pilot phase. As the first 30 patients are included during the pilot phase, randomisation weights will be 3, 4, 1 and 2, respectively. These numbers are chosen to closely match the overall 1:1:1 allocation. Randomisation will be performed with block sizes of 10 and 20, which are randomly selected.

Following randomisation, a designated study team member not involved in any other study procedures or data analysis will be aware of the randomisation outcome. This person will have access to a list of codes that permits the tACS device to deliver active or sham stimulation. Participants and all other study staff will be blinded to whether active or sham stimulation is applied. Due to the additional EEG required in the personalised treatment arm, blinding with regard to receiving standardised or personalised tACS will not be possible. However, EEG preprocessing and data analysis will be performed blinded for treatment allocation.

Intervention

tACS will be administered to participants who are randomised using the Nurostym tES device (Brainbox, Ltd, United Kingdom) by a trained member of the study team. The same tACS device and settings will be used across all three participating centres to ensure consistency of results. For all study arms, tACS will be administered at an intensity of 2.0 mA (peak-to-peak) for 30 minutes using two 5x5 cm saline-soaked electrodes while the impedance is kept below 10 kOhm. Electrode placement (described below) follows the 10-10 EEG system, ensuring consistent positioning of tACS electrodes across different stimulation days, patients and centres. The electrodes will be positioned beneath a 64-channel EEG cap. During the first treatment session, this cap will also be used for repeated EEG measurements, whereas on subsequent treatment days, it will serve solely as a reference for tACS electrode positioning. Treatment with psychoactive medication(s) that is deemed necessary for the participant will be continued as prescribed by the treating physician of the patients.

Standardised tACS

Standardised tACS will be applied with a frequency of 10 Hz, which is in the alpha frequency and is consistent with other alpha-tACS studies. [48] The tACS electrodes will be positioned over AFz and Oz, according to the 10-10 system for electrode placement (Figure 2). This electrode placement results in the generation of electrical fields in brain areas that demonstrate altered connectivity in delirium, including the dorsolateral prefrontal cortex, precuneus, and posterior cingulate cortex.[22,23] At the beginning of stimulation, the intensity will ramp up for 30 seconds to 2.0 mA peak-to-peak, while at the end of stimulation, the intensity will ramp down for 30 seconds to 0 mA.

Figure 2. Standardised approach for applying transcranial alternating current stimulation (tACS). **(A)** Representation of the electrode placement. Two 5x5 cm electrodes will be positioned over AFz (anterior) and Oz (posterior) locations, indicated by coloured squares (blue for posterior, yellow for anterior). **(B)** Visualisation of the electric field distribution in the brain during tACS with an intensity of 2 mA (peak-to-peak). The colour map represents the magnitude of the electric field (magnE), measured in volts per meter (V/m). SimNIBS software (version 4) was used for simulation.[49]

Personalised tACS

For personalised tACS, settings will be based on a computational model for delirium and a virtual trial. To achieve this, this study will utilise a computational model capable of mimicking in silico the EEG findings that have been observed in delirium. A network of neural masses with each neural mass (i.e. the smallest subsection of the network) representing a population of excitatory and inhibitory neurons in the brain will be used. By modifying the excitatory-inhibitory balance and/or subcortical input to the neural masses, different pathologies can be simulated. The model generates multiple channel EEG-like output, allowing for quantitative analysis of outcomes of different model parameters. Model parameters will be manipulated to simulate neuronal/synaptic changes during delirium as well as individual (personalised) brain activity and functional connectivity, resulting in EEG characteristics that are similar to that observed in a particular patient, amounting to a personalised disease model. Thereafter, the effect of various tACS parameters will be simulated to counter delirium mechanisms. These strategies will differ with regard to the electrode location and stimulation frequency. The different quantitative measures resulting from the model will be analysed similarly to patient EEG data, predicting which electrode placement and stimulation frequency will result in the most optimal treatment response regarding power spectrum and connectivity characteristics. In this context, optimal treatment response is defined as a change of spectral and connectivity characteristics of the model output in the direction of a healthy state. The optimal, individualised tACS protocol will thereafter be applied as personalised delirium treatment. Settings will be determined once during the first session and will remain unchanged in remaining sessions. All patients in the active treatment arm will receive tACS with an intensity of 2.0 mA (peak-to-peak) and a stimulation duration of 30 minutes.

We are currently investigating the optimal way to fit a network of neural masses to an individual patient with delirium, allowing performance of a virtual trial with the specified outcome parameters. The results of this development process will be published in a separate paper describing the details of this approach.

Sham stimulation

The procedure for sham stimulation will be identical to either standardised or personalised tACS, except for the electrical current administered. After the 5-digit pin code is entered, which enables sham stimulation, the tACS device will ramp up to 2.0 mA peak to peak for 30 seconds, stimulate for 60 seconds and ramp down for 30 seconds to 0 mA. This mimics the perception of actual tACS stimulation and improves blinding. To evaluate the effectiveness of blinding, both the participant and the researcher will be asked to guess the group allocation after the first and last treatment session (Appendix 1).

Outcomes

Pilot study outcomes

During the pilot phase, data regarding the percentage of fully completed tACS sessions will be recorded as well as increased care requirements within one hour following tACS administration. An increase in care requirement is defined as: a (medication-based) intervention (e.g., for heightened agitation or skin issues resulting from the electrodes), fixation, or transfer to unit with more advanced care (e.g., the ICU). Furthermore, duration of delirium will be recorded as defined in the secondary outcomes below. Upon analysis of these findings, adjustments to the protocol may be proposed and will be submitted to the Medical Research Ethics Committee (MREC) for approval before the start of the main study phase, if deemed necessary.

Main study primary outcome

Relative delta power

An 18-minute resting state EEG recording will be conducted by a trained clinical researcher directly before and after the first tACS session. EEG recordings will be obtained using a 64-channel Biosemi ActiveTwo EEG system with active gel electrodes (Biosemi B.V., Amsterdam, Netherlands) at a sampling rate of 2048 Hz. Active electrodes, wherein each electrode has its own amplifier, are employed to reduce artefacts due to enhanced signal-to-noise ratio. EEG data will be visually inspected for eye movement and muscle artefacts. A minimum of 80 seconds of eyes closed artefact-free data will be analysed. Data will undergo FIR bandpass filtering in the following frequency bands: delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), low beta (13-20 Hz) and high beta (20-30 Hz).

Relative delta power will be calculated by dividing the total power within the delta frequency band (0.5-4 Hz) by the total power across frequency bands from 0.5 to 20 Hz. The upper limit of the frequency band is limited to 20 Hz to reduce the impact of muscle artefacts and high-frequency noise on the relative delta power calculation.[50]

Secondary outcomes

- Delirium duration assessed by the number of days with delirium during the treatment period (up to 14 days). A delirium-positive day is defined as having an Intensive Care Delirium Screening Checklist (ICDSC)[51] score of ≥4. A score of –4 or lower on the RASS followed by an ICDSC score ≥4, is counted as a delirium day. For days where ICDSC is missing (e.g., due to limited staff availability on some weekends), days with a Delirium Observation Screening Scale (DOSS)[52] score ≥ 3 will also count as a delirium day. The DOSS is administered as standard of care.
- Delirium severity as assessed by the cumulative ICDSC score per participant recorded on days with delirium during the treatment period. In instances where ICDSC scores are unavailable, scores will be estimated using information from the electronic patient record.
- Quantitative EEG measures include peak frequency, spectral analysis and connectivity measures such as the phase lag index (PLI)[53], corrected amplitude envelope correlation (AECc [50]), and topological measures based on the minimum spanning tree (MST)[54,55].
- Length of hospital stay as assessed by the total number of days admitted to the hospital.
- Cognitive status three months after the first tACS session as assessed by the Telephone Interview for Cognitive Status Modified (TICS-M)[43,44].
- Presence and duration of sensations related to tACS treatment including tingling sensations, itching, mild transient redness of the skin and discomfort on the region of stimulation with the sensation questionnaire developed for this study (Appendix 1).
- The treatment burden, perception of receiving either sham or active tACS, and patients' perceptions of the therapeutic relationship with the researcher(s) will be evaluated using the questionnaires on feasibility, or blinding and subjective treatment experience , which have been developed for this study (Appendix 1).

Safety reporting

Adverse events (AEs)

AEs are defined as any undesirable experience occurring to a participant during the study, whether or not considered related to the experimental intervention. Given that hospitalised patients often experience AEs, only potential study-related AEs reported by the participant or observed by the study team during the timeframe of tACS treatment will be documented in the case report form (CRF). These include sensations related to tACS (i.e., itch, pain, burn, heat, iron taste, headache, neck pain, phosphenes, dizziness and nausea), behaviour suggesting of increase in delirium severity such as increase in use of antipsychotics, patient fixation, falling out of bed and self-removal of a line, tube or drain, and a possible epileptic seizure.

Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- Results in death;
- Is life threatening (at the time of the event);
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- Results in persistent or significant disability or incapacity;
- Any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

For the purpose of this study, an SAE is defined according to the definition above, within the timeframe of tACS treatment, which includes up to 24 hours after the last tACS session. It should be noted that infectious diseases such as pneumonia, wound infection, sepsis, (postoperative) haemorrhage, or laboratory disturbances, such as hyponatremia or hypokalaemia that may prolong inpatients' hospitalisation or may be life-threatening, will not be considered as an SAE. This exclusion is due to the frequency of these complications in the population being studied, which is unrelated to tACS treatment.

Statistical analysis

For the analysis of the primary study parameter, a modified intention-to-treat protocol will be used. The sole criterium for inclusion in the analysis is that a participant has completed the initial tACS session. Changes in relative delta power will be assessed using separate linear mixed models for standardised and personalised tACS compared to sham, with relative delta power as the dependent variable, time*group and study centre as fixed factors, and participant as a random factor. Data analysis will be performed blinded for treatment allocation. A significance level of $p = 0.025$ (two-tailed) will be applied to correct for type-I errors since there are two intervention groups (standardised tACS and personalised tACS). In cases of deviations from the linear mixed model, robust models and non-parametric alternatives will be considered. Functional outcomes, along with other quantitative EEG measurements and cognitive outcomes, will be analysed using non-parametric or parametric tests depending on the distribution of scaled test results. Blinding success for participants as well as researchers will be tested using a chi-square test.

Interim analysis

Pre-planned interim analyses will be conducted after the pilot study to assess the percentage of fully completed tACS sessions, increased care requirements within one hour following tACS administration, and differences in delirium duration between the active and sham tACS treatment groups. For these analyses, a Student's t-test will be employed if data follow a normal distribution, whereas a Mann-Withney test will be used for skewed distributions. Results will be shared with the MREC before proceeding with the main study phase.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this study.

Data management, monitoring and access

The handling of personal data will adhere to the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. Study data will be collected and managed using CASTOR, a secure electronic case record form (eCRF) accessible via the internet.

Investigators will be assigned personal usernames and passwords, and all data transfers will be encrypted. Only data essential to addressing the research question outlined in this protocol will be collected and stored. All data will be pseudonymised and treated confidentially. Only necessary study members will have access to this subject identification list. Investigators will electronically sign to confirm that eCRF entries are accurate and complete. Source documents will be securely stored in a locked filing cabinet, accessible only to authorised research personnel, and archived for the legally mandated period. Before the start of the study, it is agreed which documents serve as source data for eCRF. Monitoring will be conducted in accordance with national laws, guidelines, and ICH-GCP specifications. Given the low-risk intervention, there will not be an independent Data Monitoring Committee.

ETHICS AND DISSEMINATION

The study has been approved by the MREC of the Utrecht University Medical Center (23-198) and the Institutional Review Boards of participating centres. This study will be conducted according to the principles of the Declaration of Helsinki (see for the most recent version: www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations, and Acts. All substantial amendments will be notified to the local MREC. The trial results will be made accessible to the public in a peer reviewed journal, preferably open access.

Trial status

Protocol version 1.5, June 2024. The trial is currently in the recruitment phase. Initial approval of the MREC was granted in January 2024. The first participant was included in April 2024. The expected end date for the trial is April 2027.

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Authors contributions

AJCS, EVD, WDH and IT conceived the idea for the DELTES study. JVDA and DYL drafted the study protocol in close collaboration with THO, EVD and AJCS, which was critically reviewed by all authors. The manuscript was drafted by JVDA, and critically revised and approved by all other authors before submission.

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Patient consent for publication

Not applicable

Competing interests statement

None declared.

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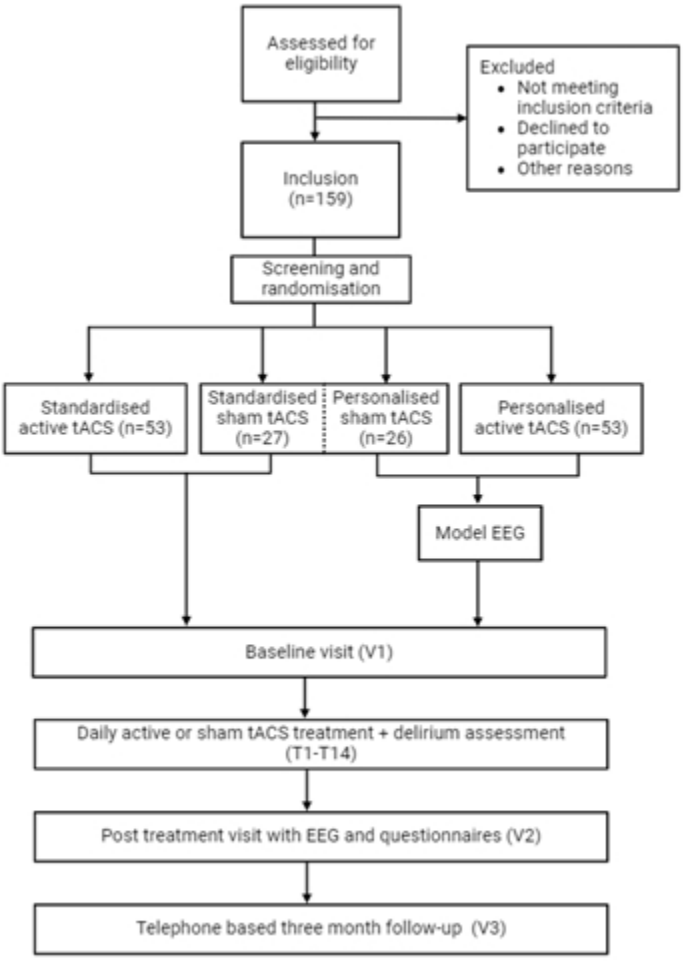

Figure 1. Study flowchart. tACS = transcranial alternating current stimulation; EEG = electroencephalography; V = visit, T= treatment.

265x340mm (38 x 38 DPI)

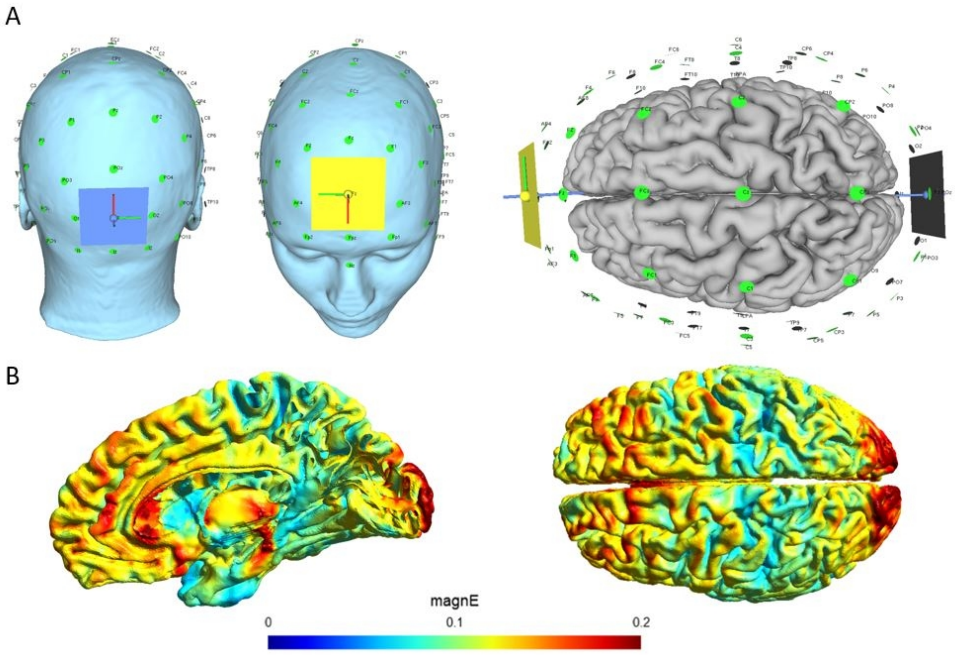

Figure 2. Standardised approach for applying transcranial alternating current stimulation (tACS). (A) Representation of the electrode placement. Two 5x5 cm electrodes will be positioned over AFz (anterior) and Oz (posterior) locations, indicated by coloured squares (blue for posterior, yellow for anterior). (B) Visualisation of the electric field distribution in the brain during tACS with an intensity of 2 mA (peak-to-peak). The colour map represents the magnitude of the electric field (magnE), measured in volts per meter (V/m). SimNIBS software (version 4) was used for simulation.49

267x181mm (96 x 96 DPI)

Appendix 1

Sensation questionnaire

Did the patient perceive anything unusual during the stimulation? Use the scale below to answer the following questions regarding different sensations and the extent to which the patient felt them.

1. Itching			
☐ none	☐ mild	☐ severe	☐ no reliable answer
2. Pain			
☐ none	☐ mild	☐ severe	☐ no reliable answer
3. Burning sensation			
☐ none	☐ mild	☐ severe	☐ no reliable answer
4. Heat sensation under electrodes			
☐ none	☐ mild	☐ severe	☐ no reliable answer
5. Iron taste			
☐ none	☐ mild	☐ severe	☐ no reliable answer
6. Headache			
☐ none	☐ mild	☐ severe	☐ no reliable answer
7. Neck pain			
☐ none	☐ mild	☐ severe	☐ no reliable answer
8. Phosphenes			
☐ none	☐ mild	☐ severe	☐ no reliable answer
9. Dizziness			
☐ none	☐ mild	☐ severe	☐ no reliable answer
10. Nausea			
☐ none	☐ mild	☐ severe	☐ no reliable answer

Only ask the following questions if sensations were perceived in questions 1 to 10.

11. When did the sensations begin?

☐ at the beginning of the stimulation (the first few minutes)

☐ in the middle of the stimulation

☐ at the end of the stimulation (the last few minutes)

12. How long did the sensations last?

☐ less than a minute

☐ several minutes

☐ longer than 5 minutes

☐ (almost) the entire stimulation

The following questions are directed to the researcher.

13. To what extent did you observe pain or discomfort in the patient during the stimulation?

☐ none ☐ mild ☐ severe ☐ no reliable answer

Only ask questions 14 and 15 if pain or discomfort was observed in question 13.

14. When did you notice the pain or discomfort in the patient?

☐ at the beginning of the stimulation (the first few minutes)

☐ in the middle of the stimulation

☐ at the end of the stimulation (the last few minutes)

15. How long did you observe the pain or discomfort in the patient?

☐ less than a minute

☐ several minutes

☐ longer than 5 minutes

☐ (almost) the entire stimulation

Blinding and subjective treatment experience questionnaire

Do you think you received real or sham (placebo) stimulation?

☐ real ☐ placebo (sham) ☐ don't know

How certain are you of your choice? (0% = not at all certain, 100% = absolutely certain) _____ %

How did you experience the contact with the researcher(s)?

excellent	☐
good	☐
neutral	☐
poor	☐
very poor	☐
don't	☐

<u>To be filled out by the researcher</u>:

Do you think the patient received real or placebo stimulation?

☐ placebo (sham)

☐ real

Experiences with tACS Treatment for Delirium

Version for patients

You have just undergone treatment with brain stimulation (tACS). We would like to hear from you about how you experienced this treatment and therefore ask you to answer the questions below. The answers will help us improve the treatment.

What did you think of the treatment?

_____
_____
_____
_____
_____

How burdensome did you find this treatment?

Very much (1)	A little (2)	Neutral (3)	Not (4)	Not at all (5)

How would you rate the feasibility of this treatment? Please rate between 1 (poor) and 10 (excellent)

Experiences with tACS Treatment for Delirium

Version for relatives

Your relative has just undergone treatment with brain stimulation (tACS). We would like to hear from you about how you experienced this treatment for your relative and therefore ask you to answer the questions below. The answers will help us improve the treatment.

What is your relationship to the patient? Circle what applies:

Spouse / partner / son / daughter / parent / guardian / conservator / mentor / other, namely _____

What did you think of the treatment for your relative?

_____
_____
_____
_____
_____

How burdensome did you find this treatment for your relative?

Very much (1)	A little (2)	Neutral (3)	Not (4)	Not at all (5)

How would you rate the feasibility of this treatment? Please rate between 1 (poor) and 10 (excellent)

Experiences with tACS Treatment for Delirium

Version for health care provider

One of your patients has just undergone treatment with brain stimulation (tACS). We would like to hear from you about how you experienced this treatment for the patient and therefore ask you to answer the questions below. The answers will help us improve the treatment.

Which healthcare provider filled out this questionnaire? Circle what applies:

Nurse / Resident physician / Specialist

What did you think of the treatment for the patient?

_____
_____
_____
_____
_____

How burdensome did you find this treatment for the patient?

Very much (1)	A little (2)	Neutral (3)	Not (4)	Not at all (5)

How would you rate the feasibility of this treatment? Please rate between 1 (poor) and 10 (excellent)

BMJ Open

DELirium treatment with Transcranial Electrical Stimulation (DELTES): study protocol for a multicentre, randomised, double-blind, sham-controlled trial

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Mental health
Keywords:	Delirium, Electroencephalography, Randomized Controlled Trial

DELirium treatment with Transcranial Electrical Stimulation (DELTES): study protocol for a multicentre, randomised, double-blind, sham-controlled trial

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ABSTRACT

Introduction: Delirium, a clinical manifestation of acute encephalopathy, is associated with extended hospitalisation, long-term cognitive dysfunction, increased mortality, and high health care costs. Despite intensive research, there is still no targeted treatment. Delirium is characterised by electroencephalography (EEG) slowing, increased relative delta power and decreased functional connectivity. Recent studies suggest that transcranial alternating current stimulation (tACS) can entrain EEG activity, strengthen connectivity, and improve cognitive functioning. Hence, tACS offers a potential treatment for augmenting EEG activity and reducing the duration of delirium. This study aims to evaluate the feasibility and assess the efficacy of tACS in reducing relative delta power.

Methods and analysis: DELTES is a randomised, double-blind, sham-controlled trial conducted across three medical centres in the Netherlands. The study comprises two phases: a pilot phase (n=30) and a main study phase (n=128). Participants are patients aged 50 years and older who are diagnosed with delirium (DSM-5-TR criteria) that persists despite treatment of underlying causes. During the pilot phase, participants will be randomised (1:1) to receive either standardised (10 Hz) tACS or sham tACS. In the main study phase, participants will be randomised to standardised tACS, sham tACS, or personalised tACS, in which tACS settings are tailored to the participant. All participants will undergo daily 30 minutes of (sham) stimulation for up to 14 days or until delirium resolution or hospital discharge. Sixty-four-channel resting-state EEG will be recorded pre- and post the first tACS session, and following the final tACS session. Daily delirium assessments will be acquired using the Intensive Care Delirium Screening Checklist (ICDSC) and Delirium Observation Screening Scale (DOSS). The pilot phase will assess the percentage of completed tACS sessions and increased care requirements post-tACS. The primary outcome variable is change in relative delta EEG power. Secondary outcomes include (1) delirium duration and severity, (2) quantitative EEG measurements, (3) length of hospital stay, (4) cognitive functioning at three months post-tACS, and (5) tACS treatment burden. Study recruitment started in April 2024 and is ongoing.

Ethics and dissemination: The study has been approved by the Medical Ethics Committee (MREC) of the Utrecht University Medical Center and the Institutional Review Boards of all participating centres. Trial results will be disseminated via peer-reviewed publications and conference presentations.

Trial registration: ClinicalTrials.gov (NCT06285721). Registered on 19-02-2024.

Strengths and limitations of this study

- Sham controlled randomised controlled trial to evaluate transcranial alternating current stimulation (tACS) as treatment for delirium.
- The analysis of electroencephalography (EEG) before and after tACS will provide insights into the neurophysiological effects of tACS in delirium.
- Inclusion of a pilot phase to assess the feasibility of tACS in a delirium population.
- Incorporation of a personalised treatment arm that tailors tACS settings to an individual participant.
- Applicability to hyperactive delirium may be limited due to the requirement for patients to complete EEG assessments.

INTRODUCTION:

Delirium, a neuropsychiatric syndrome characterised by an acute disturbance in consciousness and cognition precipitated by an medical condition such as infection or surgery, affects approximately 23% of medical inpatients.[1,2] It is associated with extended hospitalisation, long-term cognitive dysfunction, increased mortality, and increased health care costs.[3–8] There is no specific treatment for delirium itself. Current management strategies primarily target precipitating factors and employ (non-)pharmacological interventions to alleviate symptoms.[1,9] As duration of delirium is independently associated with worsened long-term cognitive outcomes and dementia, interventions to treat delirium itself are needed.[4,10,11]

Delirium is one of the clinical manifestations of acute encephalopathy, a rapidly developing pathobiological process in the brain,[12] measurable by electroencephalography (EEG). EEG power spectral analysis in patients with acute encephalopathy presenting as delirium consistently shows increased power in delta and theta bands, primarily in frontal regions, and reduced power in the alpha band, predominantly in occipital and parietal regions.[13–19] Of these changes, reduced relative delta power (0.5 - 4 Hz) is the most robust feature and can be used to classify the presence of delirium based on EEG compared to non-delirious control patients.[20,21] This shift to slow wave activity correlates with delirium severity, strengthening the evidence for a relation between these phenomena.[19] Furthermore, delirium is associated with decreased functional brain connectivity and reduced network efficiency in the alpha frequency band.[16,17] Studies using functional magnetic resonance imaging have demonstrated decreased integration and efficiency of the default mode network (DMN) in patients with postoperative delirium.[22,23] Another study showed that network alterations persist after three months and correlate with cognitive impairment, indicating an association between connectivity changes and cognitive outcomes.[24]

Recent studies in healthy individuals have demonstrated the potential of transcranial alternating current stimulation (tACS) in modulating brain activity by entrainment of specific cortical rhythms based on the applied stimulation frequency.[25–27] The administration of tACS is suggested to phase-lock large populations of neurons in the superficial layers of the cerebral cortex, inducing neural synchronisation in the corresponding frequency, and changing brain connectivity.[28,29] Studies on healthy individuals have revealed that tACS applied in the alpha frequency range can augment alpha activity and functional brain connectivity,[25,30–33] both affected during delirium.[34] Furthermore, a meta-

analysis has indicated a clear beneficial effect of tACS on cognition in other populations, including improvements in attention and working memory, [35] which are cognitive domains also affected during delirium. [1] Interestingly, a recent study with healthy volunteers showed that alpha-tACS not only augments alpha activity but also strengthens connectivity within the DMN, [25] the primary network disturbed during delirium.[22,23] Additionally, oscillatory entrainment can have cross-frequency effects, [30,36] meaning that tACS applied within the alpha frequency range can lead to a decrease in relative delta power. Taken together, tACS might be able to reduce delta activity, reinforce alpha activity and connectivity in brain regions that show altered connectivity during delirium, [22,23] potentially offering therapeutic benefits.

When applying tACS as a potential treatment for delirium, the most straightforward approach is to apply tACS in the alpha frequency range, targeting both reduced alpha power and functional connectivity seen in delirium.[15–18] However, numerous approaches in terms of stimulation location and frequency are possible, which might be equally or more effective in treating delirium than alpha-tACS. Incorporating functional brain connectivity changes of individual patients into personalised treatment could improve treatment effectiveness, reduce adverse effects, decrease the need for trial and error in clinical trials, and enhance our understanding of the mechanisms underlying treatment effects.[37] The use of computational models may allow one to infer how modifications of neuronal properties might influence emergent neuronal activity and treatment response.[38] A promising type of computational model is the neural mass model, which models brain activity of large populations of neurons.[39] Using a network of coupled neural masses, neuronal activity similar to an encephalopathic EEG has been simulated. [40] Building on this, this study will apply neural mass modelling of individual functional connectivity changes in a virtual trial to optimise treatment settings.

In the current trial, we will evaluate whether tACS normalises brain activity, specifically relative delta power, in delirium. To date, no RCTs investigated tACS as treatment for delirium, highlighting significant gaps in our understanding of the feasibility, effectiveness and the most effective application strategies. Therefore, the trial will begin with a pilot phase aimed to assess feasibility. Upon successful completion of the pilot phase, the main study phase will commence with three study arms to assess the efficacy of tACS in reducing relative delta power: a standardised treatment arm, a sham control arm and a personalised treatment arm based on a computational model and virtual trial. We hypothesise that both standardised and personalised tACS will decrease relative delta power

compared to sham tACS in delirium patients. By adopting this two-step approach, this study aim to evaluate the feasibility as well as the effectiveness of tACS in patients with delirium.

METHODS AND ANALYSIS

Study objectives

For the pilot phase, the primary objective is to evaluate the safety and tolerability of tACS in patients with delirium. The main study phase aims to determine the efficacy of a single session of standardised or personalised tACS in reducing EEG relative delta power in patients with delirium. Secondary objectives include assessment of the impact of daily standardised or personalised tACS compared to sham on the duration and/or severity of delirium, the length of hospital stay, and cognitive functioning three months after the initial tACS session.

Study design and setting

This study is a double-blind, randomised controlled trial conducted across three medical centres in the Netherlands: the University Medical Center (UMC) Utrecht, Radboud UMC and HagaZiekenhuis. To assess safety and feasibility of tACS in delirious patients, the study will start with a pilot phase in which 30 patients will be randomised in a 1:1 ratio to receive daily either standardised active tACS or sham treatment for a maximum of 14 days, or until resolution of delirium or hospital discharge.

Upon completion of the pilot phase, the main study phase will begin, introducing the personalised treatment arm. Criteria for continuing to the main study phase are defined under outcomes. All patients from the pilot phase will be included in the main study analyses. Randomisation weights will be recalculated, and participants will be allocated in an overall 1:1:1 ratio to receive either standardised tACS, personalised tACS, or sham treatment (i.e., combining personalised sham and standardised sham tACS into one arm). The baseline visit will include delirium assessment using the Delirium Interview [41], administered by a trained researcher, and reviewed by an expert delirium panel. Furthermore, information will be collected from the electronic patient record and the clinical frailty scale (CFS) [42] will be evaluated. After these assessments, the first treatment session starts which includes a 64-channel EEG measurement before and after the first tACS or sham treatment. Also, a questionnaire on sensation to assess possible adverse events of tACS, a questionnaire on feasibility and questionnaire on blinding and subjective treatment experiences (Appendix 1) will be administered. Following this, daily tACS or sham treatment visits and delirium assessments will take place for a maximum of 14 days, or until resolution of delirium or hospital discharge, whichever comes first. To account for fluctuations in delirium symptoms, resolution of delirium is defined as two consecutive

negative delirium assessments. The treatment phase will end with a close out visit including a follow-up 64-channel EEG and administration of the questionnaires on sensation, blinding and subjective treatment experiences. A brief cognitive assessment using the Telephone Interview for Cognitive status, modified version (TICS-M) [43,44] is planned at three months after the first tACS session. The study design is illustrated in Figure 1, and the study schedule is presented in Table 1.

Figure 1. Study flowchart. tACS = transcranial alternating current stimulation; EEG = electroencephalography; V = visit, T= treatment.

Sample size and statistical power

The sample size calculation is based on data obtained from a previous study that examined EEG findings in both delirious and non-delirious patients.[45] In this study, patients with delirium showed a median relative delta power of 0.59 (interquartile range (IQR) 0.47-0.71), while those without delirium had a median of 0.20 (IQR 0.17-0.26), resulting in an effect size of 0.39 (0.20 – 0.59). This study excluded patients in whom the diagnosis delirium was not certain, which may have inflated the effect size. It is therefore anticipated that both standardised and personalised tACS will lead to a more modest decrease of 0.15 in relative delta EEG power post-stimulation compared to pre-stimulation measurements. We hypothesise that personalised tACS may be superior to standardised tACS in reducing relative delta power. However, the lack of data to support this claim necessitates assuming equal effectiveness for both arms in the sample size calculation. Based on these assumptions, a sample size of 159 participants (i.e., 53 per group) was estimated using G*Power 3.1. This estimation considered an effect size of 0.15 with a standard deviation of 0.3, an alpha of 0.05, and 80% statistical power. Patients who do not complete the initial tACS session with EEG recordings will be replaced, as well as patients who withdraw consent.

Study population

In total, 159 patients aged 50 years or older with a diagnosis of delirium will be included in the study.

Inclusion criteria for eligibility

In order to be eligible to participate in this study, a participant must meet all of the following inclusion criteria:

- Age over 50 years.
- Diagnosis of delirium.
- Richmond Agitation and Sedation Scale (RASS) [46] score of -2 to +2.
- Delirium duration of at least two days prior to study inclusion, based on delirium assessments and/or descriptions in the medical and/or nursing files.
- Causes underlying delirium are being treated adequately, as assessed by the treating physician and a panel of delirium experts (i.e., psychiatrist, geriatrician and intensivist).

Exclusion criteria for eligibility

A potential participant who meets one or more of the following criteria will be excluded from participation in this study:

- Inability to conduct valid delirium screening assessment (e.g. deaf, blind) or inability to speak Dutch or English.
- A moribund state.
- Alcohol/substance abuse withdrawal or stroke as the presumed cause of delirium.
- Diagnosis of dementia, based on medical record review and/or a score of ≥4.5 on the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[47].
- Brain injury of any type (e.g. traumatic, vascular, post anoxic) in the previous six weeks.
- One or more contra-indications for tACS:
    - Large or ferromagnetic metal parts in the head (except for a dental wire).
    - Implanted cardiac pacemaker or neurostimulator.
    - Skin disease or inflammation at the stimulation sites.
    - History of epilepsy.

Inclusion criteria for randomisation

- All inclusion criteria are met.
- Diagnosis of delirium is confirmed using the Delirium Interview [41] and consultation with a delirium expert who is part of the research team (psychiatrist, geriatrician and/or intensivist).
- Written informed consent obtained from legal representative.

Patient withdrawal

If a patient and/or legal representative is wants to withdraw from the study, they can do so without any consequences. We will adhere to the definitions and guidelines stipulated in the code of conduct relating to the expression of objection by incapacitated (psycho)geriatric patients in the context of the WMO (2002). The clinician or investigator can decide to withdraw a subject from the study for urgent medical reasons. There are no expected negative effects of prematurely ending the stimulation sequence.

Procedures (time needed)	**Baseline visit (V1)**	**First treatment visit (T1)**	**Additional treatment visits (T2 up to T14)**	**Post-treatment visit (V2)**	**Follow-up visit (V3)**
Medical history[a]	X				
Physical health[a]	X				X
Current medication use[a]	X	X	X	X	X
Clinical Frailty Scale[a]	X				
Sensation questionnaire (5 min)		X		X	
Blinding and subjective treatment experience (1 min)		X		X	
Feasibility questionnaire (5 min)		X			
Delirium Interview (10 min)	X				
ICDSC (10 min)	X	X	X	X	
DOSS (5 min)[b]	X	X	X	X	
TICS-M (10 min)					X
EEG (40 min)	X[c]	X		X	
tACS (30 min)		X	X		
Estimated total duration	25 or 60 min[c]	95 min	45 min	65 min	15 min

Table 1. Overview study procedures. ICDSC = Intensive Care Delirium Screening Checklist; DOSS = Delirium Observation Screening Scale; TICS-M = Telephone Interview for Cognitive status, modified version; EEG = Electroencephalogram, tACS = transcranial altering current stimulation.

[a] = this information will be recorded as part of standard clinical care, and missing information will be requested via family and will therefore not require additional time.

[b] = only non-Intensive Care Unit (ICU) patients will be assessed using the DOSS

[c] = only the group randomised to personalised tACS will receive an EEG during the baseline visit.

Informed consent, randomisation and blinding

For surgical patients, a flyer is provided during the pre-operative screening to inform patients and their legal representatives about the study, enabling them to familiarise themselves with this study in advance and consider participation in the event of delirium occurrence. In non-surgical patients, this flyer is provided to the wards with the request to hand this to newly admitted patients. Consultants, including psychiatrists, geriatricians and neurologists, and ward physicians are asked to screen for potential participants. Upon identification of patients eligible to participate in the trial, consultants and ward physicians inform the research team. The research team will inform the patient and their legal representatives about the study. If the patient and legal representative are possibly willing to participate, the investigator provides the information letter and provides them at least one day to consider study participation. If a patient is eligible for study participation, initial informed consent will be obtained from a legal representative, as the patient may be unable to provide consent when delirious (see Appendix 2 for an example of the consent form). Legal representation is identified using a hierarchical model consistent with local and national laws and regulations. Once patients regain capacity to provide informed consent, they will be asked to provide written informed consent themselves. At any time, the patient or their legal representatives can refuse or withdraw consent for the study without providing a reason and without impacting the treatment provided.

Delirious patients who meet all inclusion criteria but none of the exclusion criteria for eligibility and randomisation will be randomised to one of the study arms. Randomisation will be conducted electronically via the Castor Electronic Data Capture (EDC) study management system (Castor, Ciwit B.V., Amsterdam, the Netherlands), using a validated block randomisation model, stratified by study centre. In the pilot phase, standardised active tACS and sham carry equal weight (1:1). Patients will be randomised with block sizes of 2 and 4. In the main study phase, four groups will be created in Castor EDC (standardised active, personalised active, standardised sham, personalised sham) with different weights, depending on the number of participants who have been randomised to the active and standardised sham groups during the pilot phase. As the first 30 patients are included during the pilot phase, randomisation weights will be 3, 4, 1 and 2, respectively. These numbers are chosen to closely match the overall 1:1:1 allocation. Randomisation will be performed with block sizes of 10 and 20, which are randomly selected.

Following randomisation, a designated study team member not involved in any other study procedures or data analysis will be aware of the randomisation outcome. This person will have access to a list of codes that permits the tACS device to deliver active or sham stimulation. Participants and all other study staff will be blinded to whether active or sham stimulation is applied. To ensure blinding during the intervention, the monitor displaying the raw ECG traces will be covered with cardboard paper before the start of the procedure for patients on continuous ECG monitoring. Due to the additional EEG required in the personalised treatment arm, blinding with regard to receiving standardised or personalised tACS will not be possible. However, EEG preprocessing and data analysis will be performed blinded for treatment allocation.

Intervention

tACS will be administered to participants who are randomised using the Nurostym tES device (Brainbox, Ltd, United Kingdom) by a trained member of the study team. The same tACS device and settings will be used across all three participating centres to ensure consistency of results. For all study arms, tACS will be administered at an intensity of 2.0 mA (peak-to-peak) for 30 minutes using two 5x5 cm saline-soaked electrodes while the impedance is kept below 10 kOhm. Electrode placement (described below) follows the 10-10 EEG system, ensuring consistent positioning of tACS electrodes across different stimulation days, patients and centres. The electrodes will be positioned beneath a 64-channel EEG cap. During the first treatment session, this cap will also be used for repeated EEG measurements, whereas on subsequent treatment days, it will serve solely as a reference for tACS electrode positioning. Treatment with psychoactive medication(s) that is deemed necessary for the participant will be continued as prescribed by the treating physician of the patients.

Standardised tACS

Standardised tACS will be applied with a frequency of 10 Hz, which is in the alpha frequency and is consistent with other alpha-tACS studies. [48] The tACS electrodes will be positioned over AFz and Oz, according to the 10-10 system for electrode placement (Figure 2). This electrode placement results in the generation of electrical fields in brain areas that demonstrate altered connectivity in delirium, including the dorsolateral prefrontal cortex, precuneus, and posterior cingulate cortex.[22,23] At the

beginning of stimulation, the intensity will ramp up for 30 seconds to 2.0 mA peak-to-peak, while at the end of stimulation, the intensity will ramp down for 30 seconds to 0 mA.

Figure 2. Standardised approach for applying transcranial alternating current stimulation (tACS). **(A)** Representation of the electrode placement. Two 5x5 cm electrodes will be positioned over AFz (anterior) and Oz (posterior) locations, indicated by coloured squares (blue for posterior, yellow for anterior). **(B)** Visualisation of the electric field distribution in the brain during tACS with an intensity of 2 mA (peak-to-peak). The colour map represents the magnitude of the electric field (magnE), measured in volts per meter (V/m). SimNIBS software (version 4) was used for simulation.[49]

Personalised tACS

For personalised tACS, settings will be based on a computational model for delirium and a virtual trial. To achieve this, this study will utilise a computational model capable of mimicking in silico the EEG findings that have been observed in delirium. A network of neural masses with each neural mass (i.e. the smallest subsection of the network) representing a population of excitatory and inhibitory neurons in the brain will be used. By modifying the excitatory-inhibitory balance and/or subcortical input to the neural masses, different pathologies can be simulated. The model generates multiple channel EEG-like output, allowing for quantitative analysis of outcomes of different model parameters. Model parameters will be manipulated to simulate neuronal/synaptic changes during delirium as well as individual (personalised) brain activity and functional connectivity, resulting in EEG characteristics that are similar to that observed in a particular patient, amounting to a personalised disease model. Thereafter, the effect of various tACS parameters will be simulated to counter delirium mechanisms. These strategies will differ with regard to the electrode location and stimulation frequency. The different quantitative measures resulting from the model will be analysed similarly to patient EEG data, predicting which electrode placement and stimulation frequency will result in the most optimal treatment response regarding power spectrum and connectivity characteristics. In this context, optimal treatment response is defined as a change of spectral and connectivity characteristics of the model output in the direction of a healthy state. The optimal, individualised tACS protocol will thereafter be applied as personalised delirium treatment. Settings will be determined once during the first session and will remain unchanged in remaining sessions. All patients in the active treatment arm will receive tACS with an intensity of 2.0 mA (peak-to-peak) and a stimulation duration of 30 minutes.

We are currently investigating the optimal way to fit a network of neural masses to an individual patient with delirium, allowing performance of a virtual trial with the specified outcome

parameters. In this phase, several strategies will be considered: a disease model tailored at multiple dimensions to the individual neurophysiology [50], a model tailored to the individual peak frequency [51] or spatial modelling of individual brain activity. The results of this development process will be published in a separate paper describing the details of this approach and the most effective strategy will be utilised in the second phase of the trial.

Sham stimulation

The procedure for sham stimulation will be identical to either standardised or personalised tACS, except for the electrical current administered. After the 5-digit pin code is entered, which enables sham stimulation, the tACS device will ramp up to 2.0 mA peak to peak for 30 seconds, stimulate for 60 seconds and ramp down for 30 seconds to 0 mA. This mimics the perception of actual tACS stimulation and improves blinding. To evaluate the effectiveness of blinding, both the participant and the researcher will be asked to guess the group allocation after the first and last treatment session (Appendix 1).

Outcomes

Pilot study outcomes

During the pilot phase, data regarding the percentage of fully completed tACS sessions will be recorded as well as increased care requirements within one hour following tACS administration. An increase in care requirement is defined as: a (medication-based) intervention (e.g., for heightened agitation or skin issues resulting from the electrodes), fixation, or transfer to unit with more advanced care (e.g., the ICU). Furthermore, duration of delirium will be recorded as defined in the secondary outcomes below. Upon analysis of these findings, adjustments to the protocol may be proposed and will be submitted to the Medical Research Ethics Committee (MREC) for approval before the start of the main study phase, if deemed necessary.

Main study primary outcome

Relative delta power

An 18-minute resting state EEG recording will be conducted by a trained clinical researcher directly before and after the first tACS session. EEG recordings will be obtained using a 64-channel Biosemi

ActiveTwo EEG system with active gel electrodes (Biosemi B.V., Amsterdam, Netherlands) at a sampling rate of 2048 Hz. Active electrodes, wherein each electrode has its own amplifier, are employed to reduce artefacts due to enhanced signal-to-noise ratio. EEG data will be visually inspected for eye movement and muscle artefacts. A minimum of 80 seconds of eyes closed artefact-free data will be analysed. Data will undergo FIR bandpass filtering in the following frequency bands: delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), low beta (13-20 Hz) and high beta (20-30 Hz). Relative delta power will be calculated by dividing the total power within the delta frequency band (0.5-4 Hz) by the total power across frequency bands from 0.5 to 20 Hz. The upper limit of the frequency band is limited to 20 Hz to reduce the impact of muscle artefacts and high-frequency noise on the relative delta power calculation.[52]

Secondary outcomes

- Delirium duration assessed by the number of days with delirium during the treatment period (up to 14 days). A delirium-positive day is defined as having an Intensive Care Delirium Screening Checklist (ICDSC)[53] score of ≥4. A score of –4 or lower on the RASS followed by an ICDSC score ≥4, is counted as a delirium day. For days where ICDSC is missing (e.g., due to limited staff availability on some weekends), days with a Delirium Observation Screening Scale (DOSS)[54] score ≥ 3 will also count as a delirium day. The DOSS is administered as standard of care.
- Delirium severity as assessed by the cumulative ICDSC score per participant recorded on days with delirium during the treatment period. In instances where ICDSC scores are unavailable, scores will be estimated using information from the electronic patient record.
- Quantitative EEG measures include peak frequency, spectral analysis and connectivity measures such as the phase lag index (PLI)[55], corrected amplitude envelope correlation (AECc [50]), and topological measures based on the minimum spanning tree (MST)[56,57].
- Length of hospital stay as assessed by the total number of days admitted to the hospital.
- Cognitive status three months after the first tACS session as assessed by the Telephone Interview for Cognitive Status Modified (TICS-M)[43,44].

- Presence and duration of sensations related to tACS treatment including tingling sensations, itching, mild transient redness of the skin and discomfort on the region of stimulation with the sensation questionnaire developed for this study (Appendix 1).
- The treatment burden, perception of receiving either sham or active tACS, and patients' perceptions of the therapeutic relationship with the researcher(s) will be evaluated using the questionnaires on feasibility, or blinding and subjective treatment experience, which have been developed for this study (Appendix 1).

Safety reporting

Adverse events (AEs)

AEs are defined as any undesirable experience occurring to a participant during the study, whether or not considered related to the experimental intervention. Given that hospitalised patients often experience AEs, only potential study-related AEs reported by the participant or observed by the study team during the timeframe of tACS treatment will be documented in the case report form (CRF). These include sensations related to tACS (i.e., itch, pain, burn, heat, iron taste, headache, neck pain, phosphenes, dizziness and nausea), behaviour suggesting of increase in delirium severity such as increase in use of antipsychotics, patient fixation, falling out of bed and self-removal of a line, tube or drain, and a possible epileptic seizure. On each treatment day, the study team will screen the electronic patient record and consult with the treating physician or nurse about any health changes since the previous tACS session. Any event potentially related to the study procedures will be classified as an AE.

Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- Results in death;
- Is life threatening (at the time of the event);
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- Results in persistent or significant disability or incapacity;

- Any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

For the purpose of this study, an SAE is defined according to the definition above, within the timeframe of tACS treatment, which includes up to 24 hours after the last tACS session. It should be noted that infectious diseases such as pneumonia, wound infection, sepsis, (postoperative) haemorrhage, or laboratory disturbances, such as hyponatremia or hypokalaemia that may prolong inpatients' hospitalisation or may be life-threatening, will not be considered as an SAE. This exclusion is due to the frequency of these complications in the population being studied, which is unrelated to tACS treatment.

Statistical analysis

For the analysis of the primary study parameter, a per-protocol analysis will be used. The sole criterion for inclusion in the analysis is that a participant has completed the initial tACS session and EEG recordings. Changes in relative delta power will be assessed using separate linear mixed models for standardised and personalised tACS compared to sham, with relative delta power as the dependent variable, time*group and study centre as fixed factors, and participant as a random factor. Data analysis will be performed blinded for treatment allocation. A significance level of $p = 0.05$ (two-tailed) will be applied. To retain sensitivity to detect potential effects in this novel area of research, no adjustment for multiple comparisons will be made. In cases of deviations from the linear mixed model, robust models and non-parametric alternatives will be considered. Subgroup analysis will be conducted by including additional fixed factors to the mixed models, such as delirium aetiology, sex and age. Functional outcomes, along with other quantitative EEG measurements and cognitive outcomes, will be analysed using non-parametric or parametric tests depending on the distribution of scaled test results. Blinding success for participants as well as researchers will be tested using a chi-square test.

Interim analysis

Pre-planned interim analyses will be conducted after the pilot study to assess the percentage of fully completed tACS sessions, increased care requirements within one hour following tACS administration, and differences in delirium duration between the active and sham tACS treatment groups. For these

analyses, a Student's t-test will be employed if data follow a normal distribution, whereas a Mann-Withney test will be used for skewed distributions. Results will be shared with the MREC before proceeding with the main study phase.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this study.

Data management, monitoring and access

The handling of personal data will adhere to the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. Study data will be collected and managed using Castor EDC, a secure electronic case record form (eCRF) accessible via the internet. Investigators will be assigned personal usernames and passwords, and all data transfers will be encrypted. Only data essential to addressing the research question outlined in this protocol will be collected and stored. All data will be pseudonymised and treated confidentially. Only necessary study members will have access to this subject identification list. Investigators will electronically sign to confirm that eCRF entries are accurate and complete. Source documents will be securely stored in a locked filing cabinet, accessible only to authorised research personnel, and archived for the legally mandated period. Before the start of the study, it is agreed which documents serve as source data for eCRF. Monitoring will be conducted in accordance with national laws, guidelines, and ICH-GCP specifications. Given the low-risk intervention, there will not be an independent Data Monitoring Committee.

ETHICS AND DISSEMINATION

The study has been approved by the MREC of the Utrecht University Medical Center (23-198) and the Institutional Review Boards of participating centres. This study will be conducted according to the principles of the Declaration of Helsinki (see for the most recent version: www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations, and Acts. All substantial amendments will be notified to the local MREC. The trial results will be made accessible to the public in a peer reviewed journal, preferably open access.

Trial status

Protocol version 1.5, June 2024. The trial is currently in the recruitment phase. Initial approval of the MREC was granted in January 2024. The first participant was included in April 2024. The expected end date for the trial is April 2027.

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Authors contributions

AJCS, EVD, WDH and IT conceived the idea for the DELTES study. JVDA and DYL drafted the study protocol in close collaboration with THO, EVD and AJCS, which was critically reviewed by all authors. The manuscript was drafted by JVDA, and critically revised and approved by all other authors before submission. (DTL, THO, DJLGS, MHEV, WDH, EVD, IT, AJCS). AJCS is the guarantor of the study.

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Patient consent for publication

Not applicable

Competing interests statement

None declared.

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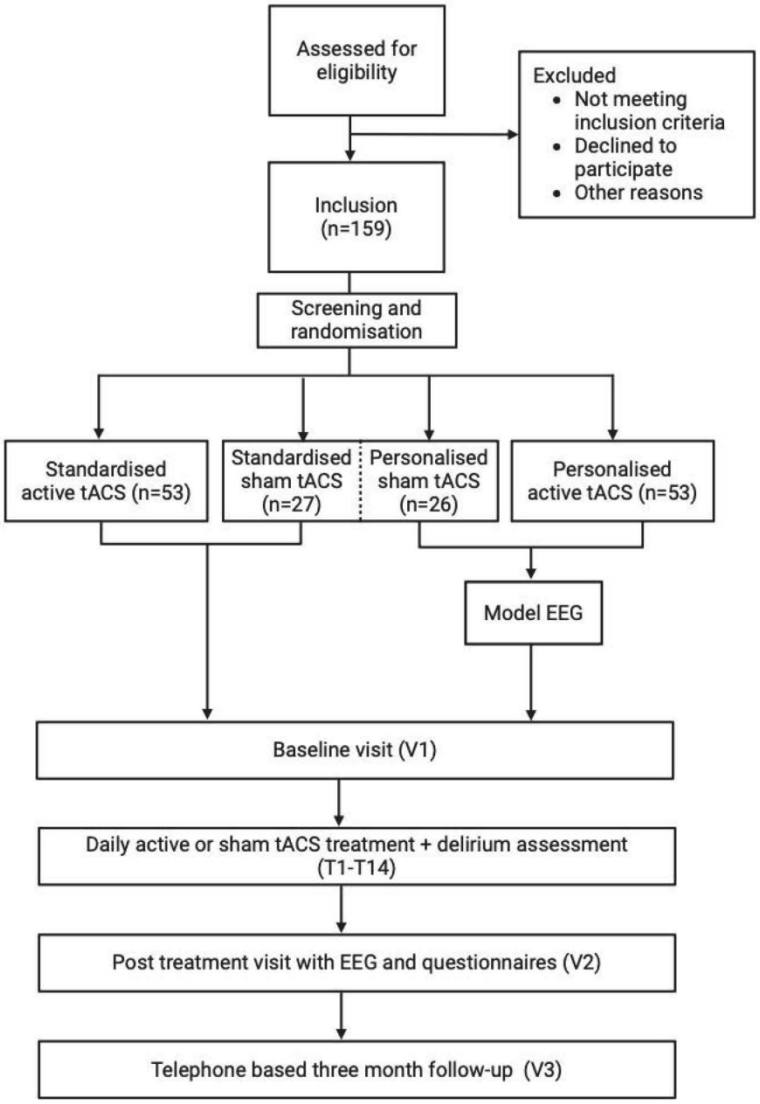

Figure 1. Study flowchart. tACS = transcranial alternating current stimulation; EEG = electroencephalography; V = visit, T= treatment.

139x181mm (300 x 300 DPI)

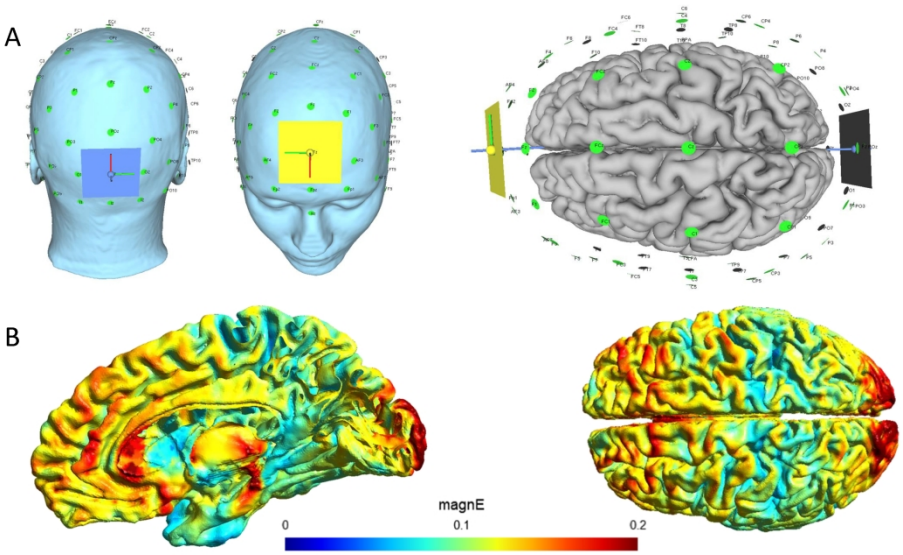

Figure 2. Standardised approach for applying transcranial alternating current stimulation (tACS). (A) Representation of the electrode placement. Two 5x5 cm electrodes will be positioned over AFz (anterior) and Oz (posterior) locations, indicated by coloured squares (blue for posterior, yellow for anterior). (B) Visualisation of the electric field distribution in the brain during tACS with an intensity of 2 mA (peak-to-peak). The colour map represents the magnitude of the electric field (magnE), measured in volts per meter (V/m). SimNIBS software (version 4) was used for simulation.49

338x190mm (300 x 300 DPI)

Appendix 1

Sensation questionnaire

Did the patient perceive anything unusual during the stimulation? Use the scale below to answer the following questions regarding different sensations and the extent to which the patient felt them.

1. Itching			
☐ none	☐ mild	☐ severe	☐ no reliable answer
2. Pain			
☐ none	☐ mild	☐ severe	☐ no reliable answer
3. Burning sensation			
☐ none	☐ mild	☐ severe	☐ no reliable answer
4. Heat sensation under electrodes			
☐ none	☐ mild	☐ severe	☐ no reliable answer
5. Iron taste			
☐ none	☐ mild	☐ severe	☐ no reliable answer
6. Headache			
☐ none	☐ mild	☐ severe	☐ no reliable answer
7. Neck pain			
☐ none	☐ mild	☐ severe	☐ no reliable answer
8. Phosphenes			
☐ none	☐ mild	☐ severe	☐ no reliable answer
9. Dizziness			
☐ none	☐ mild	☐ severe	☐ no reliable answer
10. Nausea			
☐ none	☐ mild	☐ severe	☐ no reliable answer

Only ask the following questions if sensations were perceived in questions 1 to 10.

11. When did the sensations begin?

☐ at the beginning of the stimulation (the first few minutes)

☐ in the middle of the stimulation

☐ at the end of the stimulation (the last few minutes)

12. How long did the sensations last?

☐ less than a minute

☐ several minutes

☐ longer than 5 minutes

☐ (almost) the entire stimulation

The following questions are directed to the researcher.

13. To what extent did you observe pain or discomfort in the patient during the stimulation?

☐ none ☐ mild ☐ severe ☐ no reliable answer

Only ask questions 14 and 15 if pain or discomfort was observed in question 13.

14. When did you notice the pain or discomfort in the patient?

☐ at the beginning of the stimulation (the first few minutes)

☐ in the middle of the stimulation

☐ at the end of the stimulation (the last few minutes)

15. How long did you observe the pain or discomfort in the patient?

☐ less than a minute

☐ several minutes

☐ longer than 5 minutes

☐ (almost) the entire stimulation

Blinding and subjective treatment experience questionnaire

Do you think you received real or sham (placebo) stimulation?

☐ real ☐ placebo (sham) ☐ don't know

How certain are you of your choice? (0% = not at all certain, 100% = absolutely certain) _____ %

How did you experience the contact with the researcher(s)?

excellent	☐
good	☐
neutral	☐
poor	☐
very poor	☐
don't	☐

<u>To be filled out by the researcher</u>:

Do you think the patient received real or placebo stimulation?

☐ placebo (sham)

☐ real

Experiences with tACS Treatment for Delirium

Version for patients

You have just undergone treatment with brain stimulation (tACS). We would like to hear from you about how you experienced this treatment and therefore ask you to answer the questions below. The answers will help us improve the treatment.

What did you think of the treatment?

_____

_____

_____

_____

_____

How burdensome did you find this treatment?

Very much (1)	A little (2)	Neutral (3)	Not (4)	Not at all (5)

How would you rate the feasibility of this treatment? Please rate between 1 (poor) and 10 (excellent)

Experiences with tACS Treatment for Delirium

Version for relatives

Your relative has just undergone treatment with brain stimulation (tACS). We would like to hear from you about how you experienced this treatment for your relative and therefore ask you to answer the questions below. The answers will help us improve the treatment.

What is your relationship to the patient? Circle what applies:

Spouse / partner / son / daughter / parent / guardian / conservator / mentor / other, namely _____

What did you think of the treatment for your relative?

_____
_____
_____
_____
_____

How burdensome did you find this treatment for your relative?

Very much (1)	A little (2)	Neutral (3)	Not (4)	Not at all (5)

How would you rate the feasibility of this treatment? Please rate between 1 (poor) and 10 (excellent)

Experiences with tACS Treatment for Delirium

Version for health care provider

One of your patients has just undergone treatment with brain stimulation (tACS). We would like to hear from you about how you experienced this treatment for the patient and therefore ask you to answer the questions below. The answers will help us improve the treatment.

Which healthcare provider filled out this questionnaire? Circle what applies:

Nurse / Resident physician / Specialist

What did you think of the treatment for the patient?

_____
_____
_____
_____
_____

How burdensome did you find this treatment for the patient?

Very much (1)	A little (2)	Neutral (3)	Not (4)	Not at all (5)

How would you rate the feasibility of this treatment? Please rate between 1 (poor) and 10 (excellent)

UMC Utrecht Radboudumc HagaZiekenhuis

Delirium treatment with Transcranial Electrical Stimulation

Een studie naar het effect van elektrische hersenstimulatie bij mensen met delirium (acute verwardheid)

Informatiebrief voor wettelijk vertegenwoordiger inclusief toestemmingsformulier

Versie 2.3, 01 mei 2024

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Hoofdaanvrager: UMC Utrecht

Onder leiding van Prof. dr. A.J.C. Slooter

UMC Utrecht Radboudumc HagaZiekenhuis

Geachte heer/mevrouw,

U ontvangt deze brief omdat een naaste van u is opgenomen in het ziekenhuis en momenteel acute verwardheid (ook wel delier of delirium genoemd) heeft. Wij vragen u als wettelijke vertegenwoordiger om toestemming voor deelname van uw naaste aan een medisch-wetenschappelijk onderzoek. Uw naaste is op dit moment verward, en daarom is het voor hem of haar niet mogelijk om zelf een beslissing te nemen. Zodra dit weer kan, zullen wij uw naaste zelf ook om toestemming vragen voor deelname aan het onderzoek en het gebruiken van de verzamelde gegevens.

U leest hier om wat voor onderzoek het gaat, wat het voor uw naaste betekent, en wat de voordelen en nadelen zijn. Het is veel informatie. Wilt u de informatie doorlezen en beslissen of u toestemming geeft voor deelname aan het onderzoek door uw naaste? Als u toestemming wilt geven, kunt u het formulier invullen dat u vindt in bijlage C.

Stel uw vragen

U kunt uw beslissing nemen met de informatie die u in deze informatiebrief vindt. Daarnaast raden we u aan om dit te doen:

- Stel vragen aan de onderzoeker die u deze informatie geeft.
- Praat met uw partner, familie of vrienden over dit onderzoek.
- Stel vragen aan de onafhankelijk deskundige. Voor contactgegevens zie bijlage A
- Lees de informatie op www.rijksoverheid.nl/mensenonderzoek.

1. Algemene informatie

Dit onderzoek is opgezet door het UMC Utrecht in samenwerking met het Radboudumc en het HagaZiekenhuis. Hieronder noemen we het UMC Utrecht steeds de ‘opdrachtgever’. Onderzoekers, dit kunnen ook artsen of onderzoeksverpleegkundigen zijn, voeren het onderzoek uit in het UMC Utrecht, Radboudumc en het HagaZiekenhuis. Deelnemers aan een medisch-wetenschappelijk onderzoek worden vaak proefpersonen genoemd. Zowel patiënten als mensen die gezond zijn, kunnen proefpersoon zijn. Aan dit onderzoek zullen 159 proefpersonen deelnemen. De medisch-ethische toetsingscommissie NedMec heeft dit onderzoek goedgekeurd.

2. Wat is het doel van het onderzoek?

In dit onderzoek bekijken we of stimulatie van de hersenen met een zwak elektrisch stroompje (transcraniële elektrische stimulatie of tACS) werkt als nieuwe behandeling voor delier (ook wel delirium). We vergelijken de werking van de behandeling met de werking van een niet-werkzame controlebehandeling (placebo).

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3. Wat is de achtergrond van het onderzoek?

Tijdens een ziekenhuisopname kan iemand opeens in de war raken; dit wordt delier of delirium genoemd. Een delier kan bijvoorbeeld door een operatie of ontsteking ontstaan. Deze verwardheid is meestal tijdelijk en duurt vaak enkele uren tot dagen, en soms zelfs weken. Een delier kan ernstige gevolgen hebben voor de patiënt: bijvoorbeeld langer verblijf in het ziekenhuis, langer aan de beademing of blijvende vergeetachtigheid. Daarom zijn we op zoek naar een nieuwe, effectieve behandeling voor delier.

Als je bij iemand met een delier hersengolven meet met sensoren op het hoofd (EEG), zien we dat de hersengolven zijn vertraagd. Een nieuwe behandeling die hier mogelijk iets aan kan doen is elektrische hersenstimulatie, of tACS. We weten namelijk dat deze behandeling veilig is en de hersengolven kan versnellen, alleen is dit niet bij patiënten met een delier onderzocht. Bij een deel van de patiënten doen we een standaard tACS-behandeling. Bij een ander deel kijken we of we de instellingen kunnen aanpassen op de hersengolven die we meten bij de patiënt. Hierdoor is de behandeling voor iedere persoon zo passend mogelijk (gepersonaliseerd).

4. Voorbereiding van het onderzoek

We willen eerst weten of uw naaste geschikt is om mee te doen. Daarom bekijkt de onderzoeker:

- Of een delier inderdaad aanwezig is met behulp van een vragenlijst.
- Of er redenen zijn om geen elektrische stimulatie te kunnen krijgen zoals een pacemaker, aandoeningen aan de huid of epilepsie.
- Of er andere redenen zijn om niet mee te doen aan het onderzoek zoals coma, dementie, doofheid of blindheid.

Als u toestemming geeft voor deelname van uw naaste komen we dagelijks langs voor een behandeling tijdens de ziekenhuisopname, tot maximaal 14 dagen. Drie maanden later volgt nog een telefoongesprek van ongeveer 15 minuten met een paar testjes van het geheugen.

De elektrische stimulatie kan op verschillende manieren worden ingesteld. We onderzoeken daarom of er een verschil is tussen elektrische stimulatie met standaardinstellingen, of gepersonaliseerde instellingen. Loting bepaalt of uw naaste de standaard of gepersonaliseerde behandeling krijgt. Wanneer uw naaste de gepersonaliseerde behandeling krijgt, zal de elektrische stimulatie afgestemd zijn op de hersengolven van de patiënt. Hiervoor krijgt uw naaste voorafgaand aan de behandeling een extra EEG.

Om te kunnen onderzoeken of de elektrische stimulatie (tACS) effect heeft, zal niet iedereen de actieve stimulatie krijgen. Een deel van de mensen zal elektrische stimulatie (tACS) krijgen. Een ander deel van de mensen krijgt een niet-werkzame controlestimulatie. Loting bepaalt welke behandeling uw naaste krijgt, oftewel of uw naaste de actieve of niet-werkzame controlestimulatie krijgt. U, uw naaste en de onderzoeker weten niet of uw naaste actieve of niet-werkzame controlestimulatie krijgt. Als het voor de gezondheid van uw naaste belangrijk is, kan dit wel worden opgezocht.

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5. Hoe verloopt het onderzoek?

Wanneer u toestemming geeft voor deelname van uw naaste verzamelen we een aantal basisgegevens uit het medisch dossier, zoals leeftijd, geslacht, medische voorgeschiedenis, welke behandeling uw naaste eerder tijdens de opname heeft ondergaan of momenteel ondergaat en welke medicatie uw naaste ten tijde van het onderzoek krijgt toegediend. Daarna beginnen we met een korte vragenlijst om de kenmerken van delier te meten. Wanneer uw naaste de gepersonaliseerde behandeling krijgt, zal de elektrische stimulatie afgestemd zijn op de hersengolven. Hiervoor krijgt uw naaste voorafgaand aan de behandeling een extra EEG, dit duurt ongeveer 40 minuten. Later op de dag krijgt uw naaste de eerste stimulatie. Direct voor en na de stimulatie wordt ook een EEG gemaakt om het effect van de behandeling te meten. Samen met de stimulatie duurt dit ongeveer 95 minuten.

Zolang uw naaste is opgenomen in het ziekenhuis en een delier heeft, komen we dagelijks langs voor een stimulatie, tot maximaal 14 dagen. Ook wordt er dan een korte vragenlijst afgenomen over de kenmerken van delier. In totaal zijn we ongeveer 45 minuten per dag aanwezig, maar tijdens de stimulatie (30 minuten) hoeft uw naaste niks te doen.

Wanneer uw naaste wordt ontslagen uit het ziekenhuis of het delier verdwenen is, willen we graag nog één keer een EEG maken. Daarnaast zouden we tijdens deze afspraak enkele vragenlijsten willen afnemen over de kenmerken van delier en ervaringen met de behandeling (ongeveer 45 minuten in totaal).

Tot slot willen we uw naaste, ongeveer 3 maanden na de startdatum van het onderzoek, één keer bellen voor een paar vragen over het geheugen. Deze telefonische afspraak duurt ongeveer 15 minuten.

Wat is er anders dan bij gewone zorg?

Tijdens het onderzoek krijgt uw naaste ook de normale behandeling van delier zoals medicijnen, het aanhouden van een dag-nachtritme en oorzaken zoals ontsteking behandelen (indien van toepassing). Hier bovenop komt de elektrische stimulatie. Mochten er andere behandelingen of onderzoeken moeten plaatsvinden, dan krijgen die voorrang en kunnen we de studiehandelingen bijvoorbeeld een dag overslaan.

6. Wat wordt er van uw naaste verwacht?

We willen graag dat het onderzoek goed verloopt. Daarom kan uw naaste niet ook nog aan een ander medisch-wetenschappelijk onderzoek naar delier meedoen.

Het is belangrijk dat u contact opneemt met de onderzoeker:

- als u besluit uw toestemming voor deelname aan het onderzoek in te trekken.
- als uw contactgegevens wijzigen.

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7. Van welke bijwerkingen, nadelige effecten of ongemakken kan uw naaste last krijgen?

Het meten van hersengolven met EEG

Een EEG is een middel om hersenactiviteit (hersengolven) te meten in het brein via elektroden. Uw naaste krijgt een soort badmuts met elektroden op. Het aansluiten van een EEG duurt ongeveer 10 minuten. Vervolgens zal uw naaste gevraagd worden om 15 minuten de ogen gesloten te houden en stil te liggen. Aan een EEG zijn geen risico's of bijverschijnselen verbonden. Een EEG doet geen pijn.

Afbeelding 1. De EEG-muts die wordt opgezet om de hersengolven te meten.

De behandeling met tACS (elektrische stimulatie)

Bij een behandeling met tACS (elektrische stimulatie) worden er twee kleine vochtige elektroden (dunne sponsachtige lapjes met een draadje eraan) op het hoofd geplaatst waarna een persoon dagelijks een halfuur een klein stroompje krijgt. Het apparaat dat in dit onderzoek wordt gebruikt voor tACS is de BrainBox Nurostym. Dit apparaat is gekeurd volgens de normen van de Europese Unie voor gebruik bij neuropsychiatrische aandoeningen (CE-markering).

Van deze behandeling is bekend dat het in sommige gevallen lichte bijwerkingen kan geven:

- Tijdelijk een gevoel van jeuk, branderigheid of warmte op de huid bij de elektroden. Dit trekt vanzelf weer weg.
- Hoofdpijn, moeheid of moeite met concentreren na de behandeling, die vaak binnen enkele uren weer wegtrekt.

De volgende bijwerkingen komen zeer weinig voor:

- Beschadiging (brandwondje) van de huid bij de elektroden. Deze bijwerking proberen we te voorkomen door de elektroden goed contact te laten maken met de huid.

tACS (elektrische stimulatie) wordt bij verschillende patiëntengroepen veilig gebruikt in onderzoeksverband, maar het is de eerste keer dat er onderzoek wordt gedaan naar de werking van tACS bij mensen met een delier. Daarom kunnen er ook bijwerkingen optreden die we nu nog niet weten.

Afbeelding 2. De behandeling met tACS.

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8. Deelname van wilsonbekwame proefpersonen

Het kan gebeuren dat degene die u vertegenwoordigt zich op een bepaald moment tijdens het onderzoek verzet (niet meewerkt). De onderzoeker moet het onderzoek dan direct stoppen. Het is moeilijk om precies te omschrijven wat verzet is. Voor de start van het onderzoek overleggen we met u wat wij zien als verzet. De onderzoeker zal zich houden aan de Gedragscode verzet bij wilsonbekwame (psycho)geriatrische patiënten in het kader van de Wet Medisch-Wetenschappelijk Onderzoek met mensen.

9. Wat zijn de voordelen en de nadelen als uw naaste meedoet aan het onderzoek?

Mogelijke voordelen zijn:

- De behandeling met tACS kan er mogelijk aan bijdragen dat het delier het korter duurt of minder ernstig is, maar dit is niet zeker. Omdat we nu voor het eerst tACS als behandeling voor delier onderzoeken is dit niet bekend.
- Deelname aan het onderzoek kan bijdragen aan meer kennis over de aandoening.

Mogelijke nadelen zijn:

- Uw naaste kan bijwerkingen of nadelige effecten van tACS ervaren.
- Uw naaste kan last hebben van de metingen tijdens het onderzoek.
- Meedoen aan het onderzoek kost uw naaste extra tijd.

U beslist of uw naaste meedoet aan het onderzoek. Deelname is vrijwillig. Als u geen toestemming geeft voor deelname, wordt uw naaste op de gebruikelijke manier behandeld voor zijn of haar aandoening. U kunt uw toestemming op elk moment intrekken. U hoeft niet te zeggen waarom u uw toestemming intrekt. Wel moet u dit direct melden aan de onderzoeker. De gegevens die tot dat moment zijn verzameld, worden gebruikt voor het onderzoek.

10. Wanneer stopt het onderzoek?

In deze situaties stopt voor het onderzoek voor uw naaste:

- Het einde van het onderzoek is bereikt.
- U kiest om uw toestemming in te trekken. U hoeft er niet bij te vertellen waarom.
- U, de behandelaar(s) van uw naaste of de onderzoeker(s) zien aanhoudende tekenen van verzet bij uw naaste. Tekenen van verzet kunnen verbale (spraak) of non-verbale (lichamelijke) uitingen zijn en bestaat vaak uit afwerend gedrag.
- Het UMC Utrecht, Radboudumc, HagaZiekenhuis, de overheid of de beoordelende medisch-ethische toetsingscommissie besluit om het onderzoek te stoppen.

Het gehele onderzoek is afgelopen als alle deelnemers klaar zijn.

11. Wat doen we met de gegevens van uw naaste?

Voor dit onderzoek worden de persoonsgegevens van uw naaste verzameld, gebruikt en bewaard. Het gaat om gegevens zoals naam, geslacht, contactgegevens, adres, geboortedatum en om gegevens over

de gezondheid van uw naaste. Het verzamelen, gebruiken en bewaren van deze gegevens is nodig om de vragen die in dit onderzoek worden gesteld te kunnen beantwoorden en de resultaten te kunnen publiceren.

Hoe beschermen we de privacy?
Om de privacy van uw naaste te beschermen geven wij de gegevens van uw naaste een code. Op al deze gegevens zetten we alleen deze code. De sleutel van de code bewaren we op een beveiligde plek in het ziekenhuis. Als we de gegevens van uw naaste verwerken, gebruiken we steeds alleen die code. Ook in rapporten en publicaties over het onderzoek kan niemand terughalen dat het over uw naaste ging.

Wie kunnen de gegevens van uw naaste zien?
Sommige personen kunnen wel de naam en andere persoonlijke gegevens van uw naaste zonder code inzien. Dit kunnen gegevens zijn die speciaal voor dit onderzoek zijn verzameld, maar ook gegevens uit het medisch dossier. Dit zijn mensen die controleren of de onderzoekers het onderzoek goed en betrouwbaar uitvoeren. Deze personen kunnen bij de gegevens van uw naaste komen:

- Leden van de commissie die de veiligheid van het onderzoek in de gaten houdt.
- Een controleur die door het UMC Utrecht is ingehuurd.
- Nationale toezichthoudende autoriteiten.

Deze personen houden de gegevens van uw naaste geheim. Voor inzage door deze personen vragen wij u toestemming te geven. De Inspectie Gezondheidszorg en Jeugd kan zonder uw toestemming de gegevens van uw naaste inzien.

Hoelang bewaren we de gegevens van uw naaste?
Alle studiegegevens worden in een beveiligde omgeving bewaard tot 15 jaar na het einde van het onderzoek. Daarna worden de gegevens van uw naaste vernietigd.

Mogen we de gegevens van uw naaste gebruiken voor ander onderzoek?
De gegevens van uw naaste kunnen erg waardevol zijn voor ander wetenschappelijk onderzoek op het gebied van delier of de behandeling met tACS, zowel binnen als buiten de EU. Buiten de EU gelden mogelijk andere regels voor bescherming van persoonsgegevens. Daarom vragen wij uw toestemming voor het doorsturen van de gegevens. De gegevens worden alleen gecodeerd doorgegeven en zijn niet naar uw naaste herleidbaar. Geeft u geen toestemming voor het delen van de gegevens van uw naaste? Dan kan uw naaste nog steeds meedoen aan dit onderzoek. Uw naaste krijgt dan dezelfde zorg.

Wat gebeurt er bij onverwachte ontdekkingen?
Tijdens het onderzoek kunnen we toevallig iets vinden dat niet direct van belang is voor het onderzoek maar wel voor de gezondheid van uw naaste. De onderzoeker neemt dan contact op met de specialist van uw naaste. De specialist bespreekt met u en uw naaste wat er moet gebeuren. De kosten hiervan vallen onder de zorgverzekering van uw naaste. U geeft met het formulier toestemming voor het informeren van de specialist van uw naaste.

Kunt u of uw naaste de toestemming voor het gebruik van uw gegevens weer intrekken?
U kunt uw toestemming voor het gebruik van de gegevens van uw naaste op ieder moment intrekken. Zeg dat dan tegen de onderzoeker. Maar let op: de onderzoeksgegevens die zijn verzameld tot het moment dat u uw toestemming intrekt worden nog wel gebruikt in het onderzoek. Wanneer uw naaste na het verdwijnen van het delier zijn of haar toestemming intrekt, kan hij of zij ervoor kiezen alle verzamelde gegevens te laten verwijderen.

Wilt u meer weten over de privacy van de gegevens?

- Wilt u meer weten over de rechten bij de verwerking van persoonsgegevens van uw naaste? Kijk dan op www.autoriteitpersoonsgegevens.nl.
- Heeft u als naaste vragen over uw rechten? Of heeft u een klacht over de verwerking van de persoonsgegevens van uw naaste? Neem dan contact op met degene die verantwoordelijk is voor de verwerking van uw persoonsgegevens. Voor dit onderzoek is dat:
    - Zie bijlage A voor contactgegevens.
- Als u klachten heeft over de verwerking van de persoonsgegevens van uw naaste, raden we u aan om deze eerst te bespreken met het onderzoeksteam. U kunt ook naar de Functionaris Gegevensbescherming van het ziekenhuis waar uw naaste wordt behandeld gaan. Of u dient een klacht in bij de Autoriteit Persoonsgegevens.

12. Krijgt uw naaste een vergoeding als hij of zij meedoet aan het onderzoek?

De onderzoeken, extra testen en behandeling voor het onderzoek kosten u en uw naaste niets. U en/of uw naaste wordt niet betaald voor het meedoen aan dit onderzoek.

13. Is uw naaste verzekerd tijdens het onderzoek?

Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten via het UMC Utrecht. De verzekering dekt schade door het onderzoek. In bijlage B vindt u meer informatie over de verzekering en de uitzonderingen. Daar staat ook aan wie u schade kunt melden.

14. Heeft u vragen?

Vragen over het onderzoek kunt u stellen aan de onderzoeker. Wilt u advies van iemand die er geen belang bij heeft? Ga dan naar de onafhankelijk deskundige, voor contactgegevens zie bijlage A. Hij weet veel over het onderzoek, maar werkt niet mee aan dit onderzoek. Heeft u een klacht? Bespreek dit dan met de onderzoeker of de behandelend arts. Wilt u dit liever niet? Ga dan naar de klachtenfunctionaris van uw ziekenhuis. In bijlage A staat waar u die kunt vinden.

U kunt uw beslissing nemen met de informatie die u in deze informatiebrief vindt. Daarnaast raden we u aan om al uw vragen te stellen aan de onderzoekers, over het onderzoek te praten met naasten en de informatie te lezen op www.rijksoverheid.nl/mensenonderzoek.

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15. Hoe geeft u toestemming voor het onderzoek?

Wanneer u voldoende bedenktijd heeft gehad, wordt u gevraagd te beslissen over deelname aan dit onderzoek. Indien u toestemming geeft, zullen wij u vragen deze op de bijbehorende toestemmingsverklaring schriftelijk te bevestigen. Door uw schriftelijke toestemming geeft u aan dat u de informatie heeft begrepen en instemt met deelname van uw naaste aan het onderzoek. Het handtekeningenblad wordt door de onderzoeker bewaard. U krijgt een kopie of een tweede exemplaar van deze toestemmingsverklaring.

Dank voor uw tijd.

16. Bijlagen bij deze informatie

A. Contactgegevens
B. Informatie over de verzekering
C. Overzicht onderzoekshandelingen
D. Toestemmingsformulier

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Bijlage A: contactgegevens

Als u nog vragen heeft over dit onderzoek, neemt u dan gerust contact op met een van de onderstaande onderzoeksmedewerkers:

Coördinerend onderzoeker	Julia van der A, MSc Heidelberglaan 100, 3584 CX Utrecht j.vandera-2@umcutrecht.nl Tel. (088) 756 75 23
Onderzoeker UMC Utrecht:	Prof. dr. Arjen J.C. Slooter Heidelberglaan 100, 3584 CX Utrecht A.Slooter-3@umcutrecht.nl
Onderzoeker Radboudumc:	Prof. dr. Indira Tendolkar Reinier Postlaan 10, 6525 GC Nijmegen Indira.Tendolkar@radboudumc.nl
Onderzoeker HagaZiekenhuis:	Dr. Thomas Ottens Els Borst-Eilersplein 275, 2545 AA Den Haag T.Ottens@hagaziekenhuis.nl
Onafhankelijk arts:	Dr. Maarten M.J. van Eijk, Intensivist-anesthesioloog Afdeling Intensive Care UMC Utrecht m.m.j.vaneijk-7@umcutrecht.nl

Klachten:
Als u klachten heeft kunt u dit melden aan de onderzoeker of aan uw behandelend arts. Mocht u ontevreden zijn over de gang van zaken bij het onderzoek en een klacht willen indienen dan kunt u contact opnemen met de klachtenbemiddelaars van het ziekenhuis. Heeft u vragen/klachten over de toepassing en naleving van de privacyregels, dan kunt u terecht bij de functionaris gegevensbescherming.

UMC Utrecht
De klachtenbemiddelaar is beschikbaar via tel. 088-755 62 08. Of digitaal via:
http://www.umcutrecht.nl/nl/Ziekenhuis/Ervaringen-van-patienten/Een-klacht-indienen

Contactgegevens Functionaris voor de Gegevensbescherming:
post: UMC Utrecht t.a.v. Functionaris gegevensbescherming
Huispostnummer Fac. 10.12
Postbus 85500 3508GA Utrecht
e-mail: privacy@umcutrecht.nl

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Voor meer informatie over uw rechten:
Raadpleeg de website van het UMC Utrecht voor meer informatie over uw rechten:
https://www.umcutrecht.nl/nl/Ziekenhuis/In-het-ziekenhuis/Regels-en-rechten/Rechten

HagaZiekenhuis

De klachtenfunctionarissen zijn bereikbaar via e-mail of post.
E-mail: klachten.suggesties@hagaziekenhuis.nl
Post: HagaZiekenhuis Den Haag, t.a.v. klachtenfunctionaris
Antwoordnummer 1320
2504 VB Den Haag (een postzegel is niet nodig)

U kunt uw klacht ook indienen via een digitaal formulier. Ga hiervoor naar:
https://www.hagaziekenhuis.nl/over-hagaziekenhuis/ook-goed-om-te-weten/klachten-en-suggesties/klachtenformulier/

Contactgegevens Functionaris voor de Gegevensbescherming:
E-mail: fg@hagaziekenhuis.nl
Telefoon: 070-210 0000 en vraag om doorverbonden te worden met de functionaris gegevensbescherming.

Radboudumc

De klachtenbemiddelaar is beschikbaar via: tel. (024) 361 31 91 of per post:
Radboudumc
348 Afdeling Klachtenbemiddeling
Antwoordnummer 540
6500 VC Nijmegen

U kunt uw klacht ook indienen via een digitaal formulier. Ga hiervoor naar:
https://www.radboudumc.nl/patientenzorg/uw-afspraak/meer-informatie/klachten/vier-stappen-om-een-klacht-in-te-dienen/klachtenbemiddelaar

Contactgegevens Functionaris voor de Gegevensbescherming
Radboudumc
t.a.v. Functionaris voor Gegevensbescherming
Huispost 27
Postbus 9101
6500 HB NIJMEGEN
Website Privacy: https://www.radboudumc.nl/patientenzorg/rechten-en-plichten/privacy
E-mail: gegevensbescherming@radboudumc.nl

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Bijlage B: informatie over de verzekering

Voor iedereen die meedoet aan dit onderzoek, heeft het UMC Utrecht een verzekering afgesloten. De verzekering dekt schade door deelname aan het onderzoek. Dit geldt voor schade tijdens het onderzoek of binnen vier jaar na het einde van deelname aan het onderzoek. Schade moet binnen die vier jaar aan de verzekeraar zijn gemeld.

De verzekering dekt niet alle schade. Onderaan deze tekst staat in het kort welke schade niet wordt gedekt. Deze bepalingen staan in het 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015'. Dit besluit staat in de Wettenbank van de overheid (https://wetten.overheid.nl).

Bij schade kunt u direct contact leggen met de verzekeraar.

De verzekeraar van het onderzoek is:	
Naam verzekeraar:	QBE Europe SA/NV Nederland
Adres:	Prins Bernhardplein 200, 1097 JB, Amsterdam
Telefoonnummer:	+31 (0)20 899 2700
E-mail:	info@nl.qbe.com
Polisnummer:	064457/01/2023/0000

De verzekering betaalt maximaal € 650.000 per persoon en € 5.000.000 voor het hele onderzoek € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever.

Let op: de verzekering dekt de volgende schade **niet**:

- Schade door een risico waarover we u informatie hebben gegeven in deze brief. Maar dit geldt niet als het risico groter bleek te zijn dan we van tevoren dachten. Of als het risico heel onwaarschijnlijk was.
- Schade aan de gezondheid van uw naaste die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan.
- Schade die ontstaat doordat uw naaste aanwijzingen of instructies niet of niet goed opvolgde.
- Schade aan de gezondheid van de kinderen of kleinkinderen van uw naaste.
- Schade door een behandelmethode die al bestaat. Of door onderzoek naar een behandelmethode die al bestaat.

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Bijlage C: Overzicht procedures DELTES-studie

Procedures (tijd)	Baseline visite (V1)	Eerste behandeling (T1)	Vervolg behandeling (dag 2 tot dag 14[a])	Eind van de behandeling (V2)	Telefonische visite (V3)
Vragenlijsten delier (5-15 min)	X	X	X	X	
tACS (30 min)		X	X		
EEG (40 min)	X[b]	X		X	
Vragenlijsten ervaring behandeling (10 min)		X		X	
Telefonische vragenlijst cognitie (15 min)					X
Verwachte tijdsduur	15 of 55 min	95 min	45 min	65 min	15 min

EEG = Electroencephalogram; tACS = behandeling met hersenstimulatie

[a] = afhankelijk of uw naaste nog delirant is

[b] = dit geldt alleen voor de patiënten die de gepersonaliseerde behandeling krijgen

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Bijlage D: Toestemmingsformulier vertegenwoordiger, DELTES-studie

Horende bij: Een studie naar het effect van elektrische hersenstimulatie bij mensen met delirium (acute verwardheid), DELTES-studie

Naam proefpersoon: ……..... Geb. datum: …….

- Ik heb de informatiebrief voor de proefpersoon/vertegenwoordiger gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik wil dat deze persoon meedoet.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen dat deze persoon toch niet meedoet. Ik hoef dan niet te zeggen waarom ik dat wil.
- Ik geef de onderzoeker toestemming om de behandelend arts/specialist te laten weten dat deze persoon meedoet aan dit onderzoek.
- Ik geef de onderzoeker toestemming om de specialist van deze persoon informatie te geven over onverwachte uitkomsten van het onderzoek die van belang zijn voor de gezondheid van deze persoon.
- Ik geef de onderzoekers toestemming om de gegevens van deze persoon te verzamelen en te gebruiken. De onderzoekers doen dit om alleen de onderzoeksvraag in dit onderzoek te beantwoorden.
- Ik weet dat voor de controle van het onderzoek sommige mensen toegang tot alle gegevens van deze persoon kunnen krijgen. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om de gegevens van deze persoon in te zien voor deze controle.
- Ik geef ☐ **wel** / ☐ **geen*** toestemming voor het doorsturen van gecodeerde gegevens van deze persoon in het kader van ander onderzoek naar landen buiten de EU. Ik weet dat buiten de EU mogelijk andere privacy regels gelden. Ik weet dat er voor het delen van de gegevens een gelijkwaardig beschermingsniveau zal worden afgesproken.
- Ik geef ☐ **wel** / ☐ **geen*** toestemming om de gegevens van deze persoon te bewaren om die te gebruiken voor ander onderzoek, zoals in de informatiebrief staat.
- Ik geef ☐ **wel** / ☐ **geen*** toestemming om deze persoon na dit onderzoek te vragen of hij/zij wil meedoen met een vervolgonderzoek
- Ik ga ermee akkoord dat deze persoon meedoet aan dit onderzoek.

Naam wettelijk vertegenwoordiger:……

Relatie tot de proefpersoon: ……

Handtekening: …… Datum: _____ / _____ / _____

Ik verklaar dat ik de persoon/personen hierboven volledig heb geïnformeerd over het genoemde onderzoek.

Wordt er tijdens het onderzoek informatie bekend die de toestemming van de vertegenwoordiger kan beïnvloeden? Dan laat ik dit op tijd aan deze persoon weten.

Naam onderzoeker (of diens vertegenwoordiger):…….....

Handtekening: …… Datum: _____ / _____ / _____

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* Aankruisen wat van toepassing is.

De vertegenwoordiger krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.