ISRCTN55942704 https://doi.org/10.1186/ISRCTN55942704

Assessment of characteristic disease signs and evaluation of a treatment approach with low-intensity electrical brain stimulation in persons with visual snow syndrome

Submission date
21/11/2022

Recruitment status
No longer recruiting

Registration date
19/01/2023

Overall study status
Completed

Last Edited
10/05/2023

Condition category
Nervous System Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Current plain English summary as of 13/04/2023:
Background and study aims
With this project, we aim to improve our understanding of Visual Snow Syndrome (VSS), find diagnostic markers that could be applied in a clinical setting, and evaluate a targeted non-pharmacological treatment with transcranial alternating current stimulation (tACS).
Patients with VSS suffer from severe visual disturbances and associated non-visual symptoms, such as tinnitus and concentration problems. The disorder was named after the main symptom, "Visual Snow", a flickering across the visual field, often compared to the static of an old, poorly tuned TV screen. These symptoms are distressing and lead to an impairment in everyday life. At the moment, there is no established “objective” measures to support the diagnosis, and there is no established treatment approach.
The underlying cause is not fully understood, but the results of recent studies suggest a disturbance in the brain system involved in the “filtering” of visual information.

Who can participate?
In this study, we aim to include 20 persons affected by Visual Snow Syndrome and 20 healthy control persons. We will aim to achieve the same distribution for age, gender and migraine in the control group as in the group with persons affected by Visual Snow Syndrome. The study takes place at the University of Bern in Switzerland. It is partially funded by the Swiss Headache Society and the Bangerther-Rhyner Foundation.

What does the study involve?
This study consists of two parts:
Part 1: ”Diagnostic markers of the Visual Snow Syndrome”
A) EEG:
For all the included persons, we will perform an EEG (electroencephalogram). This is a technique used to display electrical changes on the brain surface with contacts on the scalp. For this, we will install a cap with 64 contacts. We will record at rest and the following visual tasks. We will

also perform a short photic stimulation with light flashes.
B) Visual tasks:
We will ask the participants to perform a series of visual tasks. During this EEG, pupil size (with special glasses) and the heart rate (with electrodes on the chest) will be recorded. The visual tasks will be performed sitting in front of a computer, and the response will be given by pressing a button.
C) Sensory discomfort thresholds:
Sensitivity to sound will be measured by applying four different tones over headphones and changing the volume until the participants signal that this is unpleasant.
For pain, we will use a special device (thermatode) that is in contact with the skin and can gradually change the temperature (warm) until the patricipants signal that this is painful.
For light, the participants will sit in a darkened room at a defined distance from a light source while the brightness is gradually increased.

Part 2: ”Neuromodulatory treatment approach”
In this step, we would like to include only the 20 participants affected by Visual Snow Syndrome. With the transcranial alternating current stimulation (tACS) we aim to influence the communication between brain areas involved in the processing of visual information.
The participants will receive 6 sessions of tACS over 5 days (20 min per session). There will be additional 3 sessions with a sham stimulation, which means that almost no current will be applied. Still, it will cause similar side effects as the treatment condition. The participants and the investigator applying the tACS will not know which mode is being applied (sham or real stimulation), the order of the applications will be randomized.

What are the possible benefits and risks of participating?
We do not know if there are benefits such as a potential amelioration of Visual Snow Symptoms, since this application has not been investigated in persons with Visual Snow Syndrome yet.
The main side effects of tACS that have been described so far are the perception of light flashes, unpleasant sensations on the scalp, headache, dizziness, neck stiffness and back pain. No serious adverse events have been reported.
Due to the way of action, it is theoretically possible that psychiatric symptoms, seizures or a worsening of the VSS symptoms could occur, although no such events have been reported in the literature so far.

Where is the study run from?
Insel Gruppe AG (Switzerland)

When is the study starting and how long is it expected to run for?
January 2023 to December 2024

Who is funding the study?
Bangerther-Rhyner Foundation (Switzerland)
Swiss headache society

Who is the main contact?
Prof. Dr. Christoph Schankin, christoph.schankin@insel.ch

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Previous plain English summary:
Background and study aims
With this project, we aim to improve our understanding of Visual Snow Syndrome (VSS), find diagnostic markers that could be applied in a clinical setting, and evaluate a targeted non-

pharmacological treatment with transcranial alternating current stimulation (tACS).
Patients with VSS suffer from severe visual disturbances and associated non-visual symptoms, such as tinnitus and concentration problems. The disorder was named after the main symptom, "Visual Snow", a flickering across the visual field, often compared to the static of an old, poorly tuned TV screen. These symptoms are distressing and lead to an impairment in everyday life. At the moment, there is no established “objective” measures to support the diagnosis, and there is no established treatment approach.
The underlying cause is not fully understood, but the results of recent studies suggest a disturbance in the brain system involved in the “filtering” of visual information.

Who can participate?
In this study, we aim to include 20 persons affected by Visual Snow Syndrome and 20 healthy control persons. We will aim to achieve the same distribution for age, gender and migraine in the control group as in the group with persons affected by Visual Snow Syndrome. The study takes place at the University of Bern in Switzerland. It is partially funded by the Swiss Headache Society and the Bangerther-Rhyner Foundation.

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We will ask the participants to perform a series of visual tasks. During this EEG, pupil size (will special glasses) and the heart rate (with electrodes on the chest) will be recorded. The visual tasks will be performed sitting in front of a computer, and the response will be given by pressing a button.
C) Sensory discomfort thresholds:
Sensitivity to sound will be measured by applying four different tones over headphones and changing the volume until the participants signalize that this is unpleasant.
For pain, we will use a special device (thermatode) that is in contact with the skin and can gradually change the temperature (warm/cold) until the patricipants signalize that this is painful.
For light, the participants will sit in a darkened room at a defined distance from a light source while the brightness is gradually increased.

Part 2: ”Neuromodulatory treatment approach”
In this step, we would like to include only the 20 participants affected by Visual Snow Syndrome. With the transcranial alternating current stimulation (tACS) we aim to influence the communication between brain areas involved in the processing of visual information.
The participants will receive 9 sessions of tACS over 5 days (20 min per session). One of these sessions will be a sham stimulation, which means that almost no current will be applied. Still, it will cause similar side effects as the treatment condition.
Participants can be excluded due to the diagnostic or therapeutic results of the trial.

What are the possible benefits and risks of participating?
The potential benefit for participants affected by Visual Snow Syndrome could be an amelioration of their Visual Snow Symptoms.
The main side effects of tACS that have been described so far are the perception of light flashes,

unpleasant sensations on the scalp, headache, dizziness, neck stiffness and back pain. No serious adverse events have been reported.
Due to the way of action, it is theoretically thinkable that psychiatric symptoms, seizures or a worsening of the VSS symptoms could occur, although no such events have been reported in the literature so far.

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When is the study starting and how long is it expected to run for?
January 2023 to December 2024

Who is funding the study?
Bangerther-Rhyner Foundation (Switzerland)
Swiss headache society

Who is the main contact?
Prof. Dr. Christoph Schankin, christoph.schankin@insel.ch

Contact information

Type(s)
Principal investigator

Contact name
Prof Christoph Schankin

ORCID ID
https://orcid.org/0000-0003-4668-6098

Contact details
Freiburgstrasse 18
Bern
Switzerland
3010
+4131 632 21 11
christoph.schankin@insel.ch

Additional identifiers

Study information

Scientific Title
Diagnostic markers and neuromodulatory treatment approach with transcranial alternating current stimulation (tACS) for visual snow syndrome

Study objectives
Current hypothesis as of 13/04/2023:
Part 1: Diagnostic markers:
1. EEG:

1.1. Alpha power over occipital brain regions is decreased in subjects with Visual Snow Syndrome
Exploratory:
1.2. The peak-frequency of the alpha-rhythm over occipital brain regions is decreased in subjects with Visual Snow Syndrome
1.3. The “Cirp”-response between 18 and 26Hz is more pronounced in subjects with Visual Snow Syndrome
1.4. The amplitude of the mismatch potential in subjects with Visual Snow Syndrome is decreased compared to controls (Oddballtask)
2. Visual tasks:
2.1. The reaction times in subjects with Visual Snow Syndrome are prolonged compared to controls
Exploratory:
2.2. The increase in pupil size and heart rate when confronted with the Oddball in subjects with Visual Snow Syndrome is lower than in controls.
3. Sensory thresholds:
Exploratory:
3.1. All sensory discomfort thresholds in subjects with Visual Snow Syndrome are decreased compared to controls.

Part 2: Neuromodulatory approach:
1. There is an improvement in VSS-Score (density) after the stimulation
2. Object recognition of noisy images improves during and after stimulation compared to baseline (measured before stimulation)
Exploratory:
3.1. The alpha power is increased after the tACS stimulation
3.2. Depression-, sleep- and anxiety scores have lowered after tACS treatment
3.3. There is an improvement in the VSS-score or the psychiatric Score after 1 week and 1 month

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Previous hypothesis:
Part 1: Diagnostic markers:
1. EEG:
1.1. Alpha power over occipital brain regions is decreased in subjects with Visual Snow Syndrome
1.2. The peak-frequency of the alpha-rhythm over occipital brain regions is decreased in subjects with Visual Snow Syndrome
1.3. The “Cirp”-response between 18 and 26Hz is more pronounced in subjects with Visual Snow Syndrome
2. Visual tasks:
2.1. The reaction times in subjects with Visual Snow Syndrome are prolonged compared to controls
2.2. The amplitude of the mismatch potential in subjects with Visual Snow Syndrome is decreased compared to controls
2.3. The increase in pupil size and heartrate when confronted with the Oddball in subjects with Visual Snow Syndrome is lower than in controls.
3. Sensory thresholds:
3.1. All sensory discomfort thresholds in subjects with Visual Snow Syndrome are decreased compared to controls.

Part 2: Neuromodulatory approach:
1. There is an improvement in VSS-Score (density) after the stimulation
2. Object recognition of noisy images improves during and after stimulation compared to baseline (measured before stimulation)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/02/2023, Kantonale Ethikkommission (KEK) Bern (Murtenstrasse 31, 3010 Bern, Switzerland; +41 31 633 70 70; info.kek@be.ch), no ref

Primary study design
Interventional

Study design
Monocentric interventional one-armed study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Neuromodulatory treatment approach and evaluation of diagnostic marker for the Visual Snow Syndrome (a migraine related perceptual disorder).

Interventions
Current intervention as of 13/04/2023:
Part 1: ”Diagnostic markers of the Visual Snow Syndrome”
1. EEG:
For each subject (20 controls and 20 patients), we will perform a high-density EEG (64 Channels) during rest and the following visual tasks. We will also perform an additional short photic stimulation (“Chirps”) to assess the photic driving response over the occipital brain areas.
2. Visual tasks:
We will ask the subjects to perform a series of visual tasks measuring different aspects of visual processing. During this EEG and ECG will be recorded. The visual tasks will be performed sitting in front of a computer, and the response will be given by pressing a button.
3. Sensory discomfort thresholds:
Sensitivity to sound will be measured by applying four different tone frequencies over headphones and changing the volume until the discomfort threshold is found.
For pain, we will perform quantitative sensory testing (QST), assessing the pain threshold for warm temperatures with a thermatode.
For light, the subjects will sit in a darkened room at a defined distance from a light source while the brightness is gradually increased.

Part 2: ”Neuromodulatory treatment approach”
In this step, we would like to include only the 20 subjects affected by Visual Snow Syndrome. We plan the application of the transcranial alternating current stimulation (tACS) for 20 minutes two times per day (6 sessions in total). A weak (maximal 2mA), sinusoidal current is applied via external electrodes to the scalp.
The treatment will be adjusted during the stimulation according to the subjects' feedback (amelioration of symptoms or side effects). Additionally, each subject will receive 3 sessions of sham stimulation (20 minutes).

We will create three blocks with 3 sessions each (2 blocks of verum stimulation and 1 block of sham sessions). The order of these blocks will be randomized. The subjects and the investigators

applying the stimulation will be blinded.

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Previous intervention:
Part 1: ”Diagnostic markers of the Visual Snow Syndrome”
1. EEG:
For each subject (20 controls and 20 patients), we will perform a high-density EEG (64 Channels) during rest and the following visual tasks. We will also perform an additional short photic stimulation (“Chirps”) to assess the photic driving response over the occipital brain areas.
2. Visual tasks:
We will ask the subjects to perform a series of visual tasks measuring different aspects of visual processing. During this EEG, pupil size and ECG will be recorded. The visual tasks will be performed sitting in front of a computer, and the response will be given by pressing a button.
3. Sensory discomfort thresholds:
Sensitivity to sound will be measured by applying four different tone frequencies over headphones and changing the volume until the discomfort threshold is found.
For pain, we will perform quantitative sensory testing (QST), assessing the pain threshold for warm/cold temperatures with a thermatode.
For light, the subjects will sit in a darkened room at a defined distance from a light source while the brightness is gradually increased.

Part 2: ”Neuromodulatory treatment approach”
In this step, we would like to include only the 20 subjects affected by Visual Snow Syndrome. We plan the application of the transcranial alternating current stimulation (tACS) for 20 minutes two times per day over 4 consecutive days. A weak (maximal 2mA), sinusoidal current is applied via external electrodes to the scalp.
The treatment will be adjusted during the stimulation according to the subjects' feedback (amelioration of symptoms or side effects). Additionally, each subject will receive a session of sham stimulation (20 minutes). We will exclude subjects with a significant placebo effect from the study.

Intervention Type
Device

Phase
Phase II

Drug/device/biological/vaccine name(s)
Transcranial alternating current stimulation (tACS)

Primary outcome(s)
Current primary outcome measures as of 10/05/2023:
Part 1: ”Diagnostic markers of the Visual Snow Syndrome”:
In this part of the study, we will perform group comparisons between subjects with Visual Snow Syndrome and matched controls.
1. EEG:
1.1. Differences between subjects affected by VSS and controls in individual alpha-rhythm (8-13Hz) concerning power and frequency at rest and during visual stimulation over occipital electrodes (O1, O2, Oz) measured on visit 1

2. Visual tasks:
2.1. Performance in the visual tasks (discrimination blocks, detection blocks, and object recognition blocks) as measured by reaction times if the answers are correct, measured on visit 1

Part 2: “Neuromodulatory treatment approach”:
1. Differences in VSS-density (VSS Scale, Puledda et al) after verum and sham stimulation (compared to the score before the beginning of the stimulation block)
2. Differences in the noisy object recognition task between verum and sham stimulation session (compared to the score before the beginning of the stimulation block)

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Previous primary outcome measures as of 13/04/2023:
Part 1: ”Diagnostic markers of the Visual Snow Syndrome”:
In this part of the study, we will perform group comparisons between subjects with Visual Snow Syndrome and matched controls.
1. EEG:
1.1. Differences between subjects affected by VSS and controls in individual alpha-rhythm (8-13Hz) concerning power and frequency at rest and during visual stimulation over occipital electrodes (O1, O2, Oz)
2. Visual tasks:
2.1. Performance in the visual tasks (discrimination blocks, detection blocks, and object recognition blocks) as measured by reaction times if the answers are correct

Part 2: “Neuromodulatory treatment approach”:
1. Differences in VSS-density (VSS Scale, Puledda et al) after verum and sham stimulation (compared to the score before the beginning of the stimulation block)
2. Differences in the noisy object recognition task between verum and sham stimulation session (compared to the score before the beginning of the stimulation block)

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Previous primary outcome measures:
Part 1:
1. DIndividual alpha-rhythm (8-13Hz) concerning power and frequency at rest and during visual stimulation over occipital electrodes (O1, O2, Oz)
2. Performance in the visual tasks (discrimination blocks, detection blocks, and object recognition blocks) as measured by reaction times if the answers are correct
3. Mean sensory thresholds between subjects affected by VSS and controls

Part 2:
1. VSS-density (VSS Scale, Puledda et al) directly after the last stimulation session
2. Noisy object recognition task before, during, and after each stimulation session

Key secondary outcome(s)

Current secondary outcome measures as of 10/05/2023:
Part 1: ”Diagnostic markers of the Visual Snow Syndrome”:
1. EEG:
1.1. Differences in the mean alpha peak frequency over the occipital electrodes (visit 1)
1.2. Differences of amplitude between subjects affected by VSS and controls in the mean Oddball mismatch-potential (at 100–350 ms) (visit 1)
1.3. Differences in the Chirp-response (between 18 and 26Hz) between subjects affected by VSS and controls (visit 1)
2. Visual tasks:

2.1. Autonomic reaction as measured by change in pupil size and heart rate when presented with the oddball (unexpected visual stimulus) compared between subjects with VSS and controls (visit 1)
3. Sensory discomfort thresholds:
3.1. Difference in mean sensory thresholds between subjects affected by VSS and controls (visit 1)

Part 2: “Neuromodulatory treatment approach”:
1. Quality of life assessed using the SF-36 scale after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
2. Anxiety assessed using the GAD-7 scale after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
3. Insomnia severity assessed using the ISI scale after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
4. Fatigue impact assessed using the FSS scale after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
5. Sleepiness assessed using the Epworth Sleepiness Scale after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
6. Depression scores assessed using PHQ-8 after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
7. Differences in occipital alpha rhythm power between baseline (day 1) and after the last stimulation session (day 5)

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Previous secondary outcome measures as of 13/04/2023:
Part 1: ”Diagnostic markers of the Visual Snow Syndrome”:
1. EEG:
1.1. Differences in the alpha frequency over the occipital electrodes
1.2. Differences of amplitude between subjects affected by VSS and controls in the Oddball mismatch-potential (at 100–350 ms)
1.3. Differences in the Chirp-response (between 18 and 26Hz) between subjects affected by VSS and controls
2. Visual tasks:
2.1. Autonomic reaction as measured by change in pupil size and heart rate when presented with the oddball (unexpected visual stimulus) compared between subjects with VSS and controls
3. Sensory discomfort thresholds:
3.1. Difference in mean sensory thresholds between subjects affected by VSS and controls

Part 2: “Neuromodulatory treatment approach”:
1. Quality of life assessed using the SF-36 scale after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
2. Anxiety assessed using the GAD-7 scale after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
3. Insomnia severity assessed using the ISI scale after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
4. Fatigue impact assessed using the FSS scale after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
5. Sleepiness assessed using the Epworth Sleepiness Scale after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
6. Depression scores assessed using PHQ-8 after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)

7. Differences in occipital alpha rhythm power between baseline and after the last stimulation session

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Previous secondary outcome measures:
Part 1:
1. Midfrontal (electrodes Fz, F1, F2, aFz) theta oscillations (4-8Hz) during the Oddball-paradigm measured using EEG
2. Oddball-mismatch-potential (at 100–350 ms) measured using EEG
3. Chirp-response measured using EEG
4. Autonomic reaction as measured by change in pupil size and heartrate when presented with the oddball (unexpected visual stimulus)
5. Correlation between sensory thresholds and power and distribution of the alpha rhythm.

Part 2:
1. Intraindividual changes in quality of life (SF-36), anxiety (GAD-7), sleep (ISI, FSS, Epworth-Scale) and depression scores (PHQ-8) after the last stimulation (day 5), after 1 week (day 12) and 1 month (day 33)
2. Changes in the performance in the image-recognition/contrast sensitivity task after every stimulation

Completion date
30/12/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 13/04/2023:
Subjects with VSS:
1. Informed consent signed
2. Subjects with VSS should fulfill the criteria of the International Headache Society (ICDH 3, A1. 4.6)

Controls:
1. Informed consent signed
2. Matched to the subjects with VSS (sex, age and migraine)

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Previous inclusion criteria:
1. Informed consent signed
2. Subjects with VSS should fulfil the criteria of the International Headache Society (ICDH 3, A1. 4.6)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Sex
All

Key exclusion criteria
Current exclusion criteria as of 13/04/2023:
Subjects with VSS:
1. Contraindications and limitations of the MD as described in the instructions for use: implanted electrical devices, cranial implants (like metal plates or screws), skull defects or head injuries
2. Contraindications to the class of MD under investigation, e.g. known hypersensitivity or allergy to the device material (rubber or sponge materials)
3. Pregnancy
4. Skin diseases with lesions on the scalp
5. Persons who are less than 18 years old

All subjects:
6. Clinically significant concomitant disease states (like epilepsy, brain tumors, traumatic, infectious or metabolic lesions or diseases of the brain, sleep disorders)
7. Known or suspected non-compliance
8. Inability to follow the procedures of the investigation, e.g. due to language problems, psychological disorders, dementia, etc., of the subject
9. Participation in another investigation with an investigational drug or another medical device within the 30 days preceding and during the present investigation
10. Enrolment of the PI, their family members, employees and other dependent persons
11. Auditory and visual (if not correctable with glasses) impairment
12. Pharmaceutical treatment for conditions related to the central nervous system
13. Therapeutic treatment which change the excitability of the central nervous system
14. Illicit substances or other substances that modify a person's natural perception regardless of whether those are commonly understood as therapeutic drugs

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Previous exclusion criteria:
1. Implanted electrical devices, cranial implants (like metal plates) or screws, skull defects or head injuries
2. Allergy to the device material
3. Clinically significant concomitant disease states (e.g., bipolar disorder, schizophrenia, epilepsy and structural cerebral lesions and other conditions when the investigator thinks it may not be safe to include a specific patient)
4. Vulnerable subjects
5. Known or suspected non-compliance, drug or alcohol abuse,
6. Inability to follow the procedures of the investigation
7. Skin diseases with lesions on the scalp
8. Auditory or visual impairment

Date of first enrolment
13/04/2023

Date of final enrolment
26/12/2024

Locations

Countries of recruitment
Germany

Switzerland

Study participating centre
Inselspital Bern
Freiburgstrasse 18
Bern
Switzerland
3010

Sponsor information

Organisation
Insel Gruppe AG

Funder(s)

Funder type
Charity

Funder Name
Bangerther-Rhyner Foundation

Funder Name
Swiss Headache Society

Results and Publications

Individual participant data (IPD) sharing plan
The anonymzied data will be available upon reasonable request. To access the anonymized participant-level data, please contact the Sponsor-Investigator of the study (Prof Christoph Schankin) using the e-mail address provided with this application. The data (questionnaire scores, visual test scores and EEG-Data as well as information about the analysis) will be shared after the publication upon reasonable request and with previous ethics approval and, if

applicable,without any time limit. The study participants will receive a general consent. They will be informed that their anonymized data might be shared with authorities or other universities and will sign the form if they agree.

IPD sharing plan summary

Available on request