Transcranial direct current stimulation in the treatment of visual hallucinations in Charles Bonnet syndrome: A randomized placebo-controlled crossover trial.

*DaSilva Morgan, K [1 *]; Schumacher, J[1]; Collerton, D[1]; Colloby, S[1]; Elder, GJ[2]; Olsen, K[1]; ffytche, DH[3†]; Taylor, J-P[1†]*.

[1] Translational and Clinical Research Institute, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, United Kingdom

[2]Northumbria Sleep Research, Department of Psychology, Faculty of Health and Life Sciences, Northumbria University, Newcastle upon Tyne, NE1 8ST, United Kingdom

[3]Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, SE5 8AF, United Kingdom

* Corresponding author. Email address: Kat.da-silva-morgan@newcastle.ac.uk

† Joint senior authors

Key Words: Charles Bonnet syndrome; Visual Hallucinations; Non-invasive stimulation; Macular Degeneration

Financial support: This work was supported by the Macular Society (BH152932) and the NIHR Newcastle Biomedical Research Centre (BRC) based at Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University and the SLaM Mental Health BRC. Dff, DC, KO, and J-PT were supported by NIHR Programme Grants for Applied Research (RP-PG-0610-10100 - SHAPED). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The funding organisation had no role in the design or conduct of the study.

Running head: Non-invasive stimulation treatment for Charles Bonnet syndrome

Abbreviations

CBS - Charles Bonnet syndrome; EEG – electroencephalography; MMSE – Mini Mental State Examination; NEVHI - North East Visual Hallucinations Interview; NPI - Neuropsychiatric Inventory; tDCS - transcranial direct current stimulation; VH - Visual hallucinations

Abstract (Word count: 278/350)

Objective: To investigate the potential therapeutic benefits and tolerability of inhibitory transcranial direct current stimulation (tDCS) on the remediation of visual hallucinations in Charles Bonnet Syndrome (CBS).

Design: Randomized, double-masked(blind), placebo-controlled crossover trial.

Participants: Sixteen individuals diagnosed with CBS secondary to visual impairment caused by eye disease experiencing recurrent visual hallucinations.

Intervention: All participants received four consecutive days of active and placebo cathodal stimulation (current density: 0.29mA/cm^2) to the visual cortex (Oz) over two defined treatment weeks, separated by a four-week wash-out period.

Main Outcome Measures: Ratings of visual hallucination frequency and duration following active and placebo stimulation, accounting for treatment order, using a 2x2 repeated measures model. Secondary outcomes included impact ratings of visual hallucinations and electrophysiological measures.

Results: When compared to placebo treatment, active inhibitory stimulation of visual cortex resulted in a significant reduction in the frequency of visual hallucinations measured by the North East Visual Hallucinations Interview, with a moderate-to-large effect size. Impact measures of visual hallucinations improved in both placebo and active conditions suggesting support and education for CBS may have therapeutic benefits. Participants who demonstrated greater occipital excitability on electroencephalography assessment at the start of treatment were more likely to report a positive treatment response. Stimulation was found to be tolerable in all participants with no significant adverse effects reported, including no deterioration in pre-existing visual impairment.

Conclusions: Findings indicate that inhibitory tDCS of visual cortex may reduce the frequency of visual hallucinations in people with CBS, particularly individuals who demonstrate greater occipital excitability prior to stimulation. tDCS may offer a feasible, novel intervention option for CBS with no significant side effects, warranting larger scale clinical trials to further characterize its efficacy.

Charles Bonnet syndrome (CBS) is a term used to describe vivid visual hallucinations (VH) secondary to significant visual loss in the absence of psychiatric illness or cognitive impairment[1]. Visual impairment is typically bilateral but CBS can occur with monocular involvement[2]. VH can be simple (flashes of light, geometric patterns or shapes), or complex (images of people, animals, scenes etc.), although CBS is sometimes used to refer to complex hallucinations only[3]. It is estimated to occur in 11-59% of patients with significant visual loss, with up to one-third reporting VH as unpleasant, distressing and disruptive of day-to-day functioning[4]. Despite the high prevalence, there is a lack of high-quality clinical trial evidence on how to treat CBS[5].

Evidence suggests CBS is a consequence of deafferentation: loss of sensory input from the eyes resulting in spontaneous, compensatory hyper-excitability of the visual cortex that results in hallucinations[6, 7]. Neurophysiological studies of CBS using electroencephalography (EEG) provide support for increased visual cortical excitability. Reduced occipital alpha-power, often used as a proxy of visual cortical excitability[8, 9], has been observed in CBS [10], along with increased amplitudes of steady-state visual evoked potentials in response to peripheral visual stimulation[11]. Such evidence suggests that a reduction of excitability in the visual cortex may help to remediate VH.

Pharmacological interventions for CBS in the case report literature include anticonvulsants, cholinesterase inhibitors and anti-psychotics that are often found to offer little-to-no immediate or longer-term benefit[5, 7]. Furthermore, pharmacological interventions are often associated with significant side-effects[12], highlighting the need for novel therapeutic interventions.

Non-invasive transcranial direct current stimulation (tDCS) can be used to modulate activity in underlying cortical structures through the application of a weak electrical current via two or more electrodes placed on the scalp. Typically, anodal stimulation increases neuronal membrane potential and cortical excitability while cathodal stimulation is inhibitory and decreases membrane potential to reduce cortical excitibilty[13]. Previous case studies have demonstrated therapeutic benefits of occipital cathodal tDCS in the treatment of VH in schizophrenia and depression[14, 15]. In these studies, repeated stimulation sessions resulted in reductions to (or complete cessation of) intrusive and distressing hallucinations. However, a randomized control trial in Lewy body dementia (LBD) found that occipital cathodal tDCS was well tolerated but did not ameliorate VH[16].

No studies have investigated the use of tDCS versus a placebo in the treatment of CBS. The objective of the present study was to determine the potential therapeutic benefit of repeated sessions of inhibitory cathodal tDCS of visual cortex compared to placebo. Improvement in the overall 'severity' of VH might relate to a reduction in how often VH occur, how long each VH episode lasts (duration) or how unpleasant or distressing VH are (VH impact). For this study we have focused on temporal aspects of VH (frequency and duration) as the primary outcome measures as they are readily quantifiable and associated with clinically relevant negative outcomes in CBS[4]. We also wanted to establish whether treating CBS by reducing visual cortical excitability might lead to potential adverse effects on visual function which is already impaired by eye disease. In addition, we used EEG recordings to investigate whether occipital activity could be used as a biomarker of treatment response or to predict therapeutic benefit.

Method

Participants

CBS related to significant visual loss was diagnosed using Teunisse criteria[1], modified to include simple as well as complex hallucinations (i.e. *complex or simple* VH in the absence of hallucinations in other modalities, delusions, impaired insight or concurrent psychiatric or neurodegenerative illness). For inclusion in the trial, participants needed to be experiencing VH a minimum of three times per week. Participants were recruited from ophthalmology services across North-East England and from a Macular Society database of members interested in research participation. Global cognitive function was assessed using the Mini Mental State Exam adapted for blind participants (MMSE-Blind; maximum score = 27)[17]. Only participants with an MMSE-blind score ≥24 were included to ensure participants were cognitively intact and did not have dementia. Depressive symptoms were assessed using the 15-item Geriatric Depression Scale (GDS)[18]. Participants with higher GDS scores (>10) suggestive of clinical depression, or with a history of moderate-to-severe cerebrovascular disease or epilepsy were excluded.

All participants provided written informed consent, and ethical approval was granted by the local Research Ethics and NHS Research and Development Committees (ref: 17/NE/0131). This study was conducted in concordance with the tenets of the Declaration of Helsinki and is registered at www.isrctn.com under the identifier ISRCTN16758036. In addition to the tDCS trial, the study included a pilot phase to identify optimal tDCS stimulation parameters in a separate group of CBS participants and structural and functional imaging studies comparing CBS with control eye disease patients, reported elsewhere[19].

Trial Design

The trial used a randomized, double-masked(blind), placebo-controlled crossover design at a single site (Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, UK). All participants received four days of either active or placebo tDCS across one week administered in the participant's own home. Participants then underwent the converse treatment (i.e. active then placebo or placebo then active). In order to avoid potential stimulation carry-over effects, a minimum washout period of 4-weeks was implemented between the two treatment weeks. Prior to treatment (Day 1; location: Newcastle University) participants underwent visual hallucination, electroencephalography (EEG) and visual function assessments. A follow-up EEG was performed immediately after the final stimulation session on Day 4 (location: participant's home), while repeat visual hallucination and visual function assessments were performed on Day 5 (location: Newcastle University). Figure 1 presents an overview of the design. The order in which active/placebo stimulation was delivered was randomized using an online randomization tool (www.randomization.com) and counterbalanced by an independent statistician (SC). Allocation codes were kept secure and only viewable by the independent statistician. A pre-programmed stimulator was used to ensure investigator and participant were masked to stimulation type.

[Figure 1]

Sample Size

No comparable studies have been conducted in CBS to inform a power-analysis. Using G*Power 3.1[20] we found a total sample size of 15 would allow detection of between-group

differences with a large effect size (Cohen's d effect size $d_z = 0.8$) in a two-tailed matched-pairs *t*-test with an alpha level of 0.05 at 80% power.

Intervention

We used tDCS stimulation parameters from the open label pilot phase of the study that examined real-time effects of different intensities and stimulation sites on VH phenomenology in CBS participants with continuous hallucinations. Stimulation was delivered using an 8-channel Starstim 8 integrated tCS/EEG neurostimulator system (Neuroelectrics, Barcelona, Spain) using 3.14cm^2 electrodes soaked in conductive gel. Electrodes were placed according to the 10-20 electrode placement system[21], with the cathodal electrode placed over Oz and bilateral anodal electrodes placed over F3 and F4, held in place by a neoprene cap (Figure 2). Stimulation was delivered at a current density of 0.29mA/cm^2 at the cathodal electrode, with a return stimulation split 50% at each anode (0.16mA/cm2 each). On Day One, in order to reduce study burden and assess initial tolerability of stimulation, participants received a shortened stimulation session: four 5-minute blocks (including a 20-second ramp-up/down period at the start and end of each block) separated by 2-minute intervals in which no stimulation occurred (20 minutes stimulation in total). On days 2-4, stimulation was given in six 5-minute blocks separated by 2-minute intervals (30 minutes stimulation in total). Short stimulation blocks were used in order to most closely replicate stimulation used during the pilot optimization study. During placebo stimulation, direct current was administered for the first and last 20-seconds (ramp-up and ramp-down periods), with the same intensity as active stimulation to generate scalp sensations similar to those at the start and end of active stimulation but without producing sustained neuromodulatory effects.

[Figure 2]

Outcomes

Primary outcomes

For the purpose of this study, temporal aspects of VH (VH frequency and duration ratings) from the North-East Visual Hallucination Interview (NEVHI)[22] and Neuropsychiatric Inventory hallucination subscale (NPI^{hall})[23] were used as primary treatment outcomes. The measures were compared before and after each stimulation week (day 1 and day 5 – see Figure 1) to look for a reduction in frequency or duration following active stimulation that was not present following placebo stimulation.

The NEVHI is a semi-structured interview designed to investigate VH phenomenology, occurrence and impact. Quantitative scores were assigned to VH frequency (1 = 'less than every few months', 2 = 'every few months', 3 = 'every few weeks', 4 = 'every few days', 5 = 'every few hours', 6 = 'every few minutes', 7 = 'every few seconds', 8 = 'continuously – present throughout the day') and duration (1 = 'seconds', 2 = 'minutes', 3 = 'hours', 4 = 'continuous while awake'). The NPI is designed for dementia studies and typically completed by care-givers. For the present study it was completed by the participants themselves, focusing on the hallucination subscale (NPI^{hall}). The NPI^{hall} frequency rating was used as a primary outcome (1 = 'occasionally – less than once per week', 2 = 'often - about once per week', 3 = 'frequently - several times per week but less than every day', 4 = 'very frequently – once or more per day').

Secondary Outcomes

Visual Hallucinations – Impact measures

The NEVHI asked participants to indicate which VH phenomena they found most distressing and provide a separate numerical rating for how frightening or upsetting the hallucination was (range 0-10) and how annoying/irritating the hallucination was (range 0-10). NPI^{hall} severity was also used as a secondary outcome (1 = 'mild – hallucinations present but seem harmless' 2 = 'moderate - hallucinations are distressing and disruptive', 3 = 'marked – hallucinations are very disruptive and a major source of behavioral disturbance'). Also included as secondary outcomes were the NPI^{hall} total score (NPI^{hall} frequency and severity scores multiplied, range 1 – 12) and the NPI^{hall} distress scale (0-5; from 'not at all' to 'very severely/extremely' distressing).

Electroencephalography

Focal occipital electroencephalography (EEG) was recorded using a Starstim 8-Channel tCS/EEG data acquisition system (Neuroelectrics, Barcelona, Spain) immediately prior to the first stimulation session and immediately after the final stimulation session in each treatment week. Eight Ag/AgCl Pi-electrodes (P7, PO7, O1, Oz, O2, PO8, P8 and F3) were placed according to the international 10-20 system within a neoprene cap over occipital and occipital-temporal regions, with a single electrode over the left dorsolateral prefrontal cortex (DLPFC, F3). Reference and ground were taken from the left earlobe and all impedances were kept below 5 kOhms. Data were sampled at 500Hz from DC to 250Hz. Resting-state EEG activity was recorded during alternating 30-second blocks with the participant's eyes open and closed[24] for five-minutes. During eyes-open blocks the participant was asked to look straight ahead to reduce eye-movement related artefacts. Participants were monitored by the investigator during the recording to ensure adherence to the protocol.

Visual Function

In order to assess potential adverse effects of inhibitory stimulation on visual function[25], visual assessments were performed before and after stimulation (day 1 and 5 of each stimulation week) using the computerized Freiburg visual acuity and contrast sensitivity tests[26].

Tolerability and side effects

Following the final session of stimulation, participants were asked to report any side effects experienced during the course of stimulation, including rating side effect severity on a scale of 0 (not present) to 10 (severe). They were also asked whether they thought the stimulation that week had been active or placebo.

EEG Analysis

Pre-processing of EEG data was performed separately for eyes-closed and eyes-open data using the EEGLAB toolbox (version 14) in Matlab. Briefly, EEG data were bandpass-filtered (1-80 Hz), notch-filtered around 50 Hz, and split into non-overlapping 2-second epochs. After visual inspection and exclusion of noisy channels or epochs with gross artefacts independent component analysis was applied and artifactual components rejected. The first 40 artefact-free epochs from each participant were used for further analysis.

Power spectral density was computed in Matlab using Bartlett's method with a Hamming window for frequencies from 2-45 Hz for each occipital electrode and epoch and averaged. Mean power was calculated for standard EEG frequency bands: delta (2-4 Hz), theta (4-5.5

Hz), pre-alpha (5.5-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and slow gamma (30-45 Hz), normalized by total power across the power spectrum. Alpha reactivity was calculated according to the following formula[27]:

$$\text{alpha reactivity} = \frac{\text{alpha power eyes closed} - \text{alpha power eyes open}}{\text{alpha power eyes closed}}$$

where alpha power was the relative power within a frequency bin around the individual alpha peak frequency ±2Hz in electrodes O1, Oz and O2. Individual alpha peak frequencies were defined from eyes closed data as the peak in an extended alpha frequency range (5.5-15 Hz) to allow for possible alpha slowing in CBS patients.

Statistical analysis

Statistical tests were carried out using the Statistical Package for the Social Sciences (SPSS, version 26, IBM corp, Armonk, NY). Outcome measures were examined in a repeated-measures analysis of variance (ANOVA) with treatment day (pre-stimulation day 1, post stimulation day 5) as a within-subject factor and treatment order (active stimulation week first, placebo stimulation week first) as a between-subjects factor. Treatment effect size was estimated using Cohen's f statistic and Omega^2, which provides an unbiased estimate of population variances ideal for smaller samples.

Within-subject analysis of outcome measures was also conducted comparing day 1 pre- and day 5 post-stimulation ratings for active and placebo weeks using the Mann-Whitney U test due to the non-normal distribution of the data.

Results

Participant flow

Participants were recruited between February 2018 and November 2019. Participant recruitment and allocation are illustrated in Figure 1.

Demographics

Sixteen participants with CBS completed the study (10 Female; 6 Male). Sample demographics are described in Table 1. Details of CBS hallucinations at study onset are presented in Table 2 and measures of VH frequency, duration and impact at different trial timepoints in Table 3. Before either active or placebo stimulation, the median NEVHI frequency of VH (rating = 5) corresponded to participants reporting VH every few hours.

[Table 1]

[Table 2.]

Primary Outcomes

Repeated-measures ANOVA demonstrated that participant ratings of VH frequency on the NEVHI were significantly reduced following active stimulation compared to placebo ($F(1,14) = 9.95$, $p = .007$) with a moderate to large effect size (Cohen's $f = .75$; partial $Omega^2 = .36$) independent of treatment order ($F(1,14)=.007$, $p=.94$). No significant difference in VH duration ($F(1,14)=1.647$, $p=.22$) or NPI^{hall} Frequency ($F(1,14)=3.50$, $p=.08$) between active and placebo stimulation was observed when accounting for treatment order. The raw NEVHI and NPI^{hall} ratings for each participant are illustrated in Figure 3 together with post-stimulation - pre-stimulation rating differences (a negative number indicates an improvement after stimulation). For NEVHI frequency in the active condition, ratings in most

participants either improved 1 point or had no change (one participant improved 2 points). In contrast, in the placebo condition most participants did not change, with 2 deteriorating and 4 improving. We wondered if the response to tDCS might be related to how long a participant had experienced CBS. However, there was no association between improvement in NEVHI frequency and length of time since CBS diagnosis (Spearman's correlation rho = 0.05, p=0.43). The mean duration of CBS in those participants that improved 1 or 2 rating points (3.1±2.9 years) was no different to those that had no change in rating (3.7±4.0 years; t=0.354, p=0.73).

Secondary Outcomes

Whilst significant within-subject differences were observed between pre- and post-stimulation ratings in both active and placebo treatment weeks (see Table 3), they did not differ between active and placebo treatment weeks in a repeated-measures ANOVA model (NEVHI irritation, NEVI distress, NPI^{hall} total, NPI^{hall} severity, NPI^{hall} distress all *p>.05* accounting for treatment order*).*

[Table 3.]

[Figure 3.]

Electroencephalography

Significant decreases in relative Delta power (z = -2.12, *p*=.034) and theta-alpha ratio (z = -2.02, *p*=.044) and a significant increase in Pre-Alpha power (z = -2.59, *p*=.010) were observed following active stimulation compared to pre-stimulation recordings (Table 4). A significant increase in Alpha reactivity (z =-2.02, *p*=.044) was observed following placebo stimulation (Table 4). However, no significant differences comparing active and placebo

treatment in a repeated-measures ANOVA model were observed for any relative power band (p>.05).

[Table 4].

Participants who went on to report reduced frequency of VH (responders) had significantly lower relative occipital alpha power preceding active stimulation (U= 9, z =-2.10, *p*=.038) and alpha reactivity (U= 6, z=-2.44, *p*=.013) compared to non-responders. This was also found using an average of pre-stimulation EEG power (before both active and placebo), with significantly lower overall relative alpha power (U=9, z=-2.01, *p*=.036) and alpha reactivity (U=10, z=-1.98, *p*=.047) in responders and a shift in peak frequency to the pre-alpha band (Figure 4). However, no relationship was observed between post-stimulation change in band-power and change in VH frequency scores (all p>.05).

[Figure 4.]

Visual Function

No significant changes in visual acuity or contrast sensitivity were observed pre- versus post-stimulation (day 1 versus day 5) in the active or placebo stimulation weeks (Table 5) or in a repeated-measures ANOVA controlling for treatment order (F(1,16) = .89, *p*=.441).

[Table 5]

Safety and Tolerability

tDCS was well tolerated by all participants with no significant, persisting side effects reported. The most frequently reported side effect during both active and placebo weeks was a tingling sensation from one or more electrodes (75% of participants following active, 68.8% placebo). Headaches were reported in 43.8% of participants following active stimulation compared to 6.3% following placebo (z = -2.45, *p*=.014) but were successfully

alleviated by over-the-counter analgesics. No significant differences between active and placebo stimulation were observed for other side effects including: itching, hot sensations on the scalp and sleepiness. Neither participants nor investigators were able to accurately distinguish active and placebo stimulation.

Discussion

Active inhibitory stimulation of the visual cortex over four consecutive days was found to significantly reduce the frequency of VH in people with CBS. As most participants reported VH occurring multiple times a day at enrolment, the reduction in frequency translated to VH only being reported 1-2 times a day or every few days following active stimulation. Below we discuss the wider implications of the findings for the treatment of VH in CBS.

Mechanism of action

The spatial extent of cortical inhibition from a cathode located at Oz in our participant group is unknown; however, based on visual cortical anatomy and biophysical modeling we anticipate maximal inhibition would be over the representation of the central visual field in the primary visual cortex (V1) and its immediate surrounding areas (V2/V3). These areas are thought to be hyper-excitable and spontaneously active in patients with CBS, particularly in those with simple hallucinations[6]. Complex hallucinations are related to more lateral and ventral occipital/occipito-temporal regions anterior to the occipital pole[28] and unlikely to have been directly inhibited by the cathode at Oz, but it may be that inhibition in V1/V2 had effects higher in the visual hierarchy through a reduction in feed-forward signals.

Cortical atrophy has previously been observed to distort tDCS current flow, potentially affecting current distribution through targeted structures and subsequent treatment effectiveness[29, 30]. Bilateral reductions in both grey and white matter are

associated with eye disease[31, 32] and were also found in a structural imaging study of the participants reported here[19]. It is possible the effect of tDCS may have been impacted by these cortical changes, potentially explaining inter-subject variation in VH improvement following tDCS and inter-subject variation of EEG measures. Another factor to consider is the focal nature of the stimulation in this study, which used smaller electrodes with a less diffuse field of stimulation than previous similar studies[14-16]. Future investigations may benefit from individualized structural and fMRI data to help localize cortical targets and model current flow to maximize stimulation efficacy[33].

We looked for signatures of reduced cortical excitability post-stimulation in the EEG to provide supportive evidence of the therapeutic mechanism. However, no changes to cortical activity were detected when comparing active to placebo stimulation and EEG measures did not correlate with changes in VH ratings. Previous studies in healthy participants without hallucinations or migraineurs have found changes in the alpha band following cathodal stimulation[34, 35]. More stimulation sessions were used in these studies (e.g. 12 sessions in Rocha[35] rather than 4 in our study) and it is possible that more sessions of tDCS over a longer timeframe may be required to produce detectable changes in the EEG. A further consideration is that the high variation in baseline occipital EEG activity across participants reduced the ability to detect significant change. The EEG spectrum in responders is also atypical, with a shift of the peak spectral power from the alpha band to lower frequencies (Figure 4). The reason for this shift is unclear but it suggests a focus on frequencies below the alpha band is required to detect tDCS changes in CBS.

Reduced occipital alpha power is often used as an indicator of increased visual cortical excitability[8, 9] and decreased alpha reactivity may indicate higher baseline occipital excitability (reduced alpha) during the eyes-closed state. Our finding that participants with

pre-existing reduced occipital alpha power and alpha reactivity where more likely to respond to tDCS supports a link between CBS and visual cortical excitability. The finding suggests that those patients with higher cortical excitability are more likely to benefit from inhibitory tDCS.

Efficacy

Our findings are consistent with evidence of a reduction in VH using inhibitory occipital tDCS in patients with schizophrenia and major depression[14, 15]. In contrast, Elder[16] noted that inhibitory occipital stimulation over four consecutive days did not lead to significant beneficial effects on VH when compared to placebo in patients with LBD. However, the mechanism of VH in LBD may differ from that in CBS or schizophrenia.

We did not find an effect of tDCS on the duration of VH. Evidence from studies of VH in LBD suggests VH duration and frequency are linked to different functional alterations[36]. VH frequency is linked to dysregulated, spontaneous activity that is more likely to be influenced by tDCS than the increases in connectivity and sustained activation that are linked to VH duration.

In contrast to VH frequency measured by the NEVHI, VH frequency measured by NPI^{hall} did not show a significant tDCS effect. This may reflect the different composition and psychometric properties of the two scales, with a more restricted range of ratings and detail captured by the NPI^{hall} frequency measure.

Clinical relevance

A survey of people with CBS and factors associated with unpleasant, intrusive, or distressing hallucinations suggested that effective treatment may not require the complete cessation of VH[4]. Changes to the frequency, duration or impact of VH may be sufficient to make CBS tolerable. None of the participants experienced cessation of their hallucinations in the current study but it may be that the reduction in frequency found is sufficient to shift CBS to a more benign form.

Our study has focused on CBS associated with eye disease but the same mechanism is thought to underlie VH in optic nerve disease and lesions of the visual pathways. Inhibitory repetitive transcranial magnetic stimulation (rTMS) over the occipital cortex has been found in case report literature to be effective treatment for VH following occipital stroke[37]. It may be that inhibitory tDCS over the visual cortex is also effective in CBS related to disorders affecting visual pathways beyond the eye.

VH effects not directly related to tDCS

Elder[16] noted caregiver-based ratings of NPI^{hall} VH severity improved following both active and placebo stimulation in LBD. The current study had similar findings with improvements to VH severity (NPI^{hall}), distress, and irritation (NEVHI) regardless of treatment week. It is possible that improvements to these emotional aspects of VH following both stimulation weeks may have been the consequence of increased social interaction, support, and awareness of CBS. Social isolation has been implicated in the formation of CBS hallucinations through lower sensory stimulation and mental vulnerability[7]. Indeed, an exacerbation of CBS hallucinations, in particular the frequency of VH, was reported in

connection with increased loneliness and isolation as a result of the COVID-19 pandemic[38]. In the present study, participants received regular contact and were actively encouraged to discuss the impact of their VH while being provided access to further information and reassurance about CBS. This indicates that increased social interaction, support groups or talking therapies, combined with treatments such as tDCS, may help reduce the emotional impact and frequency of VH.

Tolerability and adverse effects on visual function

The current study provides further evidence for the tolerability of tDCS. In keeping with previous research[29, 39] and contrasting with pharmacological approaches, only mild, transient, side effects were reported which were easily treated by over-the-counter analgesics. Contrary to previous reports that inhibitory stimulation of the visual cortex can result in reduced static contrast sensitivity[25], no adverse effect on visual acuity or contrast sensitivity was observed following stimulation in this study. Indeed, our open label study of continuous CBS hallucinations found subjective improvement to vision in some participants during stimulation as the portion of visual field containing the hallucinations shifted or constricted to allow better use of their intact visual field.

Strengths and limitations

While the sample size in this study is small, it constitutes the largest intervention study of its type performed in CBS to-date. Furthermore, a positive effect of tDCS treatment was observed with a medium-to-large effect size, indicating reasonably robust, clinically significant findings that are theoretically translatable to larger samples. However, the study

did not address the longevity of these benefits. Comparable pre-stimulation ratings of VH regardless of treatment order suggest any positive effects of tDCS were short-lived, returning to baseline values during the 4-week wash-out period. The study also did not address whether increasing the number of stimulation sessions or treatment weeks might lead to additional improvement. Further work will be required before tDCS could be considered for wider clinical use as a treatment for CBS. The findings at this stage might therefore be considered proof-of-concept for tDCS as a treatment for CBS, rather than a definitive trial.

There are currently no assessment tools aimed specifically at measuring clinically significant changes to VH symptoms following treatment. Both the NEVHI and NPI^{Hall} measure VH frequency and duration using crude ordinal categories based on retrospective reports and may lack the sensitivity to detect changes to domains considered relevant to the patient. Real-time digital diaries or time sampling methods may help better characterize changes in VH in future studies. Existing scales also lack adequate provision for assessing factors such as the intrusiveness of hallucinations (e.g., how much of the visual field they interfere with or how difficult they are to ignore) which, considering the restricted visual field in individuals with CBS, may significantly impact the disruptiveness and emotional impact of VH. This is an important treatment outcome to consider for future studies.

Finally, the current study focused on EEG changes to occipital activity only. Differential EEG activity and connectivity changes across more distal cortical regions, including parietal and frontal areas have been found in CBS[40] and future studies should investigate if tDCS leads to widespread changes using high-density EEG recordings.

Inhibitory tDCS of the visual cortex may provide beneficial therapeutic effects to temporal aspects of VH in people with CBS, particularly in individuals who demonstrate

greater baseline occipital excitability prior to stimulation as measured by EEG. tDCS may offer a low-cost intervention option for CBS with minimal side effects, warranting larger scale trials to confirm its efficacy and optimum parameters for wider clinical use.

Figure legends

Figure 1. *Participant flow demonstrating study crossover design and procedure. [a]Participants outside study travel radius; [b] One participant lost to follow-up so excluded from final analysis. Day 1 and Day 5 assessments included primary and secondary outcome measures from the Neuropsychiatric Inventory (NPI^{hall}) and North East Visual Hallucinations Interview (NEVHI).*

Figure 2. *Electrode set up including battery powered stimulator [A] connected to bilateral anodal electrodes placed over F3 and F4 each stimulating at 0.5mA[B] and cathodal electrode placed over visual cortex (Oz) stimulating at 1mA [C].*

Figure 3. *Visual hallucination ratings in the Neuropsychiatric Inventory (NPI^{hall}) and North East Visual Hallucinations Interview (NEVHI) in each stimulation week for: NPI^{hall} total (A), NPI^{hall} distress (B) and NEVHI frequency (C) (left) and treatment change scores (post-pre; right). Negative post-pre scores indicate improvement to hallucination ratings. * p<0.05; **p<0.01; ns: not significant.*

Figure 4. *Comparison of occipital power spectral density (PSD) of treatment responders and non-responders based on an average of recordings performed prior to both active and placebo stimulation.*

References

1. Teunisse RJ, Cruysberg JR, Hoefnagels WH, et al. Visual hallucinations in psychologically normal people: Charles Bonnet's syndrome. *Lancet.* 1996;347:794-7.
2. Tan CS, Sabel BA, Goh KY. Visual hallucinations during visual recovery after central retinal artery occlusion. *Arch Neurol.* 2006;63:598-600.
3. ffytche DH. Visual hallucinatory syndromes: past, present, and future. *Dialogues Clin Neurosci.* 2007;9:173-89.
4. Cox TM, ffytche DH. Negative outcome Charles Bonnet syndrome. *Br J Ophthalmol.* 2014;98:1236-9.
5. O'Brien J, Taylor JP, Ballard C, et al. Visual hallucinations in neurological and ophthalmological disease: pathophysiology and management. *J Neurol Neurosurg Psychiatry.* 2020;91:512-9.
6. Burke W. The neural basis of Charles Bonnet hallucinations: a hypothesis. *Journal of Neurology, Neurosurgery and Psychiatry (London).* 2002;73:535-41.
7. Menon GJ, Rahman I, Menon SJ, Dutton GN. Complex visual hallucinations in the visually impaired: the Charles Bonnet Syndrome. *Surv Ophthalmol.* 2003;48:58-72.
8. Thut G, Nietzel A, Brandt SA, Pascual-Leone A. Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *J Neurosci.* 2006;26:9494-502.
9. Romei V, Brodbeck V, Michel C, et al. Spontaneous fluctuations in posterior alpha-band EEG activity reflect variability in excitability of human visual areas. *Cereb Cortex.* 2008;18:2010-8.
10. Hanoglu L, Yildiz S, Polat B, et al. Therapeutic Effects of Rivastigmine and Alfa-Lipoic Acid Combination in the Charles Bonnet Syndrome: Electroencephalography Correlates. *Curr Clin Pharmacol.* 2016;11:270-3.
11. Painter DR, Dwyer MF, Kamke MR, Mattingley JB. Stimulus-Driven Cortical Hyperexcitability in Individuals with Charles Bonnet Hallucinations. *Curr Biol.* 2018;28:3475-80 e3.
12. Collerton D, Taylor JP. Advances in the treatment of visual hallucinations in neurodegenerative diseases. *Future Neurol.* 2013;8:433-44.
13. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *Neuroscientist.* 2011;17:37-53.
14. Shiozawa P, da Silva ME, Cordeiro Q, et al. Transcranial direct current stimulation (tDCS) for the treatment of persistent visual and auditory hallucinations in schizophrenia: a case study. *Brain Stimul.* 2013;6:831-3.
15. Koops S, Sommer IEC. Transcranial direct current stimulation (tDCS) as a treatment for visual hallucinations: A case study. *Psychiatry Res.* 2017;258:616-7.
16. Elder GJ, Colloby SJ, Firbank MJ, et al. Consecutive sessions of transcranial direct current stimulation do not remediate visual hallucinations in Lewy body dementia: a randomised controlled trial. *Alzheimers Res Ther.* 2019;11:9.
17. Reischies FM, Geiselmann B. Age-related cognitive decline and vision impairment affecting the detection of dementia syndrome in old age. *Br J Psychiatry.* 1997;171:449-51.
18. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res.* 1982;17:37-49.
19. Firbank MJ, daSilva Morgan K, Collerton D, et al. Investigation of structural brain changes in Charles Bonnet Syndrome. *Neuroimage Clin.* 2022;35:103041.
20. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods.* 2009;41:1149-60.
21. Jasper HH. The ten-twenty electrode system of the international federation. *Electroencephalography and Clinical Neurophysiology.* 1958;10:371-3.
22. Mosimann UP, Collerton D, Dudley R, et al. A semi-structured interview to assess visual hallucinations in older people. *Int J Geriatr Psychiatry.* 2008;23:712-8.

23. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology.* 1994;44:2308-14.
24. Jobert M, Wilson FJ, Ruigt GS, et al. Guidelines for the recording and evaluation of pharmaco-EEG data in man: the International Pharmaco-EEG Society (IPEG). *Neuropsychobiology.* 2012;66:201-20.
25. Antal A, Nitsche MA, Paulus W. External modulation of visual perception in humans. *Neuroreport.* 2001;12:3553-5.
26. Bach M. The Freiburg Visual Acuity test--automatic measurement of visual acuity. *Optom Vis Sci.* 1996;73:49-53.
27. Wan L, Huang H, Schwab N, et al. From eyes-closed to eyes-open: Role of cholinergic projections in EC-to-EO alpha reactivity revealed by combining EEG and MRI. *Hum Brain Mapp.* 2019;40:566-77.
28. ffytche DH, Howard RJ, Brammer MJ, et al. The anatomy of conscious vision: an fMRI study of visual hallucinations. *Nature Neuroscience.* 1998;1:738-42.
29. Brunoni AR, Nitsche MA, Bolognini N, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.* 2012;5:175-95.
30. Minjoli S, Saturnino GB, Blicher JU, et al. The impact of large structural brain changes in chronic stroke patients on the electric field caused by transcranial brain stimulation. *Neuroimage Clin.* 2017;15:106-17.
31. Boucard CC, Hernowo AT, Maguire RP, et al. Changes in cortical grey matter density associated with long-standing retinal visual field defects. *Brain.* 2009;132:1898-906.
32. Hernowo AT, Prins D, Baseler HA, et al. Morphometric analyses of the visual pathways in macular degeneration. *Cortex.* 2014;56:99-110.
33. Esmaeilpour Z, Shereen AD, Ghobadi-Azbari P, et al. Methodology for tDCS integration with fMRI. *Hum Brain Mapp.* 2020;41:1950-67.
34. Puanhvuan D, Nojima K, Wongsawat Y, Iramina K. Effects of repetitive transcranial magnetic stimulation and transcranial direct current stimulation on posterior alpha wave. *IEEJ Transactions on Electrical and Electronic Engineering.* 2013;8:263-8.
35. Rocha S, Rodrigues MCA, Mendonca MB, et al. Could cathodal transcranial direct current stimulation modulate the power spectral density of alpha-band in migrainous occipital lobe? *Neurosci Lett.* 2021;742:135539.
36. D'Antonio F, Boccia M, Di Vita A, et al. Visual hallucinations in Lewy body disease: pathophysiological insights from phenomenology. *J Neurol.* 2022.
37. Rafique SA, Richards JR, Steeves JK. rTMS reduces cortical imbalance associated with visual hallucinations after occipital stroke. *Neurology.* 2016;87:1493-500.
38. Jones L, Ditzel-Finn L, Potts J, Moosajee M. Exacerbation of visual hallucinations in Charles Bonnet syndrome due to the social implications of COVID-19. *BMJ Open Ophthalmol.* 2021;6:e000670.
39. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Res Bull.* 2007;72:208-14.
40. Piarulli A, Annen J, Kupers R, et al. High-Density EEG in a Charles Bonnet Syndrome Patient during and without Visual Hallucinations: A Case-Report Study. *Cells.* 2021;10.