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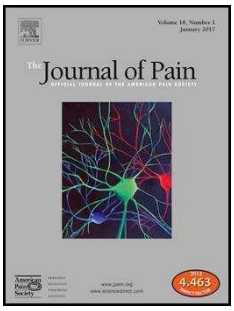

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Title page

Title: Transcranial alternating current stimulation at alpha frequency reduces pain when the intensity of pain is uncertain.

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Short running title: tACS at alpha frequency reduces pain

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Highlights

- Application of alpha tACS over somatosensory regions influences perceived pain
- Alpha tACS compared to sham lowers both perceived pain intensity and unpleasantness
- However, uncertainty about pain intensity moderates this effect
- Perceived pain was lower during alpha tACS, only when pain intensity was uncertain
- Alpha tACS has the potential to alleviate pain, particularly when pain is uncertain

Abstract

Alpha activity directly before pain onset has been implicated in pain experience with higher pre-stimulus alpha associated with lower reported pain. However, expectations about pain intensity also seem to affect pre-stimulus alpha activity. To date, evidence for a relationship between alpha activity and pain experience has been largely correlational. Transcranial alternating current stimulation at alpha frequency (alpha tACS) permits direct manipulation of alpha activity and therefore an examination of the potential causal relationship between alpha activity and pain. We investigated whether somatosensory alpha tACS could reduce pain experience and whether this was influenced by uncertainty about pain intensity. In a within-subjects design, perceived pain intensity and unpleasantness were assessed in 23 participants during alpha tACS and sham stimulation. Visual cues preceding the pain stimulus were used to manipulate uncertainty. A significant tACS * uncertainty *

stimulus intensity interaction was found for reported pain intensity ($F_{2,44}$ = 4.50; p = .017; Partial Eta^2 = .17) and unpleasantness ($F_{1,22}$ = 4.78; p = .040; Partial Eta^2 = .18). Pain experience during the application of somatosensory alpha tACS was significantly lowered compared to sham stimulation, but only when the intensity of an upcoming stimulus was uncertain.

Perspective

To our knowledge, this is the first study to suggest that somatosensory alpha tACS might lead to a reduction in pain. Interventions targeting alpha activity may have the potential to alleviate chronic pain. However, a patient's expectation about the intensity of upcoming pain must also be taken into account.

Key words: Pain, transcranial alternating current stimulation (tACS), alpha oscillations, somatosensory, expectation

Introduction

The experience of pain is highly subjective and influenced by a variety of factors including cognition, emotions, and context[35,48]. These factors can exert their influence during pain but also before pain onset, as illustrated by the phenomenon of placebo analgesia where an expectation of pain relief is followed by lower pain ratings[25,57]. Pain experience is also affected by uncertainty about the intensity of upcoming pain. Uncertainty leads to higher reported pain intensity[31,46], higher reported anxiety[46], and stronger capture of attention[11,30,36]. Moreover, uncertainty about the effectiveness of pain treatment impacts treatment outcome[6]. For instance, uncertainty about the effectiveness of a painkiller led to a significant increase in painkillers requested, a higher amount of painkiller was needed to achieve a similar reduction in pain[49].

Pain experience is also affected by neural activity before pain onset[45,47]. Alpha activity, a type of oscillatory neural activity (8-13Hz), has been studied in the context of pain for over 25 years[3,13]. Higher pre-stimulus somatosensory alpha activity (alpha directly before pain onset) and resting-state alpha activity (alpha during rest) is related to lower reported pain intensity[2,38,58]. Importantly, alpha activity appears to be influenced by expectations about pain intensity. A placebo-induced expectation of pain relief not only leads to lower pain ratings but also increased resting-state alpha activity[25]. In contrast, uncertainty about pain intensity led to a larger reduction of pre-stimulus alpha in the anterior insula[16], implicated in the emotional-cognitive processing of pain.

To date, evidence for a relationship between somatosensory alpha activity and pain experience has been largely correlational. If, and how alpha activity might influence pain experience remains unclear. A promising approach to investigating a

potential causal relationship between somatosensory alpha activity and pain experience is the application of transcranial alternating current stimulation at alpha frequency (alpha tACS) to modulate alpha activity[21,22]. TACS is used to directly modulate oscillatory neural activity in a frequency-specific manner[9,22]. During the application of tACS at a certain frequency neural activity at this particular frequency synchronizes with the tACS signal, reflecting neural entrainment (online effect of tACS)[8,51,55]. Neural entrainment also depends on the frequency characteristics of the neural network of interest. Neural entrainment is most effective when the tACS frequency matches the dominant frequency of the neural network[26]. Somatosensory neural activity has a dominant frequency within the alpha-band[29,56]. Thus, somatosensory alpha tACS should result in optimal alpha entrainment. Alpha tACS was found to increase alpha power during stimulation[20] and after tACS offset[28,37,61,63]. However, these studies applied tACS over parietal-occipital brain regions[20,28,37,61,63]. Direct evidence for an effect of somatosensory alpha tACS on somatosensory alpha activity is lacking. Furthermore, evidence for an effect of alpha tACS on somatosensory perception is limited. So far, only two studies[15,19] suggest that alpha tACS applied over the somatosensory cortex affects non-painful somatosensory perception. To our knowledge, no studies have yet investigated the effects of somatosensory alpha tACS on pain experience. However, a reduction of perceived pain has been found for rhythmic auditory and visual stimulation at alpha frequency[12].

This study addressed the effect of alpha tACS on pain experience in an experimental pain setting. In a sham-controlled design, we investigated whether somatosensory alpha tACS could reduce pain, and if this was influenced by uncertainty about pain intensity. As higher somatosensory alpha activity has been

related to lower perceived pain[2,58] it was predicted that somatosensory alpha tACS would reduce pain experience. Finally, the relationship between fear of pain, pain catastrophizing, and the effect of alpha tACS on pain experience was assessed. Higher fear of pain and pain catastrophizing are associated with higher reported pain in healthy volunteers and patients with chronic pain[23,44,53,64], and may affect pain treatment outcomes[7,50,60,62].

Methods

Participants

Twenty-six healthy right-handed volunteers took part in the study (mean age ± SD = 21.4 ± 4.7 years; 22 female). All participants met the inclusion criteria of being aged 18 or older, free of any pain at the time of testing, and not using any psychopharmacological agents. Participants were free from any contraindications for the application of tACS and pressure pain (e.g., any wounds or other skin conditions on fingers and scalp, seizures/epilepsy, cardio-vascular conditions, severe headaches/migraines, and any type of metallic foreign bodies or medical implants). Three participants were removed from the final analysis as they only completed one of the two sessions. Where two of these participants failed to attend the second session, the third participant did attend the second session but requested for the alpha tACS to be turned off within the first minutes of the pressure pain task as the participant was experiencing an itchy sensation on the skin. This resulted in an N of 23 for the final analysis. All participants provided signed informed consent before taking part in the study. The study was approved by the ethics committee of the School of Psychology at the University of Leeds.

Pain stimuli

To induce experimental pain, pressure pain was administered using a custom-built MRI-compatible pressure pain stimulator (manufactured by DancerDesign, St. Helens, UK). The pressure stimuli were delivered using a bespoke program running under E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). A circular probe, centrally placed to cover an equal area of nail and skin, was lowered onto the fingernail bed to deliver pressure to the middle finger of the left hand. During the task participants received a series of pressure stimuli at three different pressure intensities: 1) non-painful, light touch (rating of 2/10 on a 11-point numerical rating scale - NRS); 2) pain threshold, the point where the pressure stimulation becomes painful for the first time (rating of 4/10 on the NRS); and 3) moderately painful, but still tolerable (rating of 7/10 on the NRS). These three levels were established for each participant individually for each of the two sessions using a ramping procedure (ascending method of limits). The ramping procedure was carried out twice and the average was used for the stimuli in the experimental task. Stimulus duration was 4s for non-painful, 5s for pain threshold, and 6s for moderately painful stimuli. These three different durations were used to control for the difference in length of the ramping-up period: the higher the pressure intensity, the longer the ramping-up period. Based on piloting, it was decided to use these durations to ensure similar durations of stimulation at maximum intensity for all stimulus intensities.

Visual stimuli

To manipulate certainty about the intensity of the pressure stimulus prior to stimulus onset, each pressure stimulus was preceded by a visual cue. Three different visual cues were used (a green triangle, a blue circle, and a yellow square).

In the certain expectation condition, each visual cue was paired with a particular pressure stimulus intensity, resulting in visual cues that were predictive of the upcoming pressure intensity. In the uncertain condition, the same three visual cues were used. However, in this condition the visual cues were randomly combined with a pressure stimulus level, resulting in visual cues that were not predictive of the pressure intensity of the upcoming stimulus (Fig. 1).

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Figure 1

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TACS

TACS was administered for the entire duration of the pressure pain task, using a battery-driven constant current stimulator (DC Stimulator PLUS, NeuroConn GmbH, Ilmenau, Germany) and two 5x5 cm rubber electrodes, placed in saline-soaked sponges and attached with a rubber band. Alpha tACS consisted of a sinusoidal waveform with a frequency of 10Hz, and a peak-to-peak current intensity of 1mA. Impedance was kept below 55 kΩ. Two tACS electrodes were placed bilaterally over the somatosensory scalp region at electrode location CP3 and CP4 (based on EEG 10-20 electrode placement system) as in Gundlach et al.[19]. Alpha tACS was ramped up for 10s and was turned off when the pressure pain task was completed.

TACS (and transcranial electrical stimulation (tES) in general) is characterised by a mild sensation on the scalp predominantly confined to the beginning of the stimulation[14]. Therefore, in this study an active sham condition was used to ensure a

similar sensation for the verum and sham condition. For the sham condition, stimulation was applied for a brief period at the beginning of the task only, to minimise any potential effect of the sham stimulation on pain but at the same time make the sham condition indistinguishable from the verum stimulation. Whereas tACS at alpha activity was applied for the verum stimulation, transcranial random noise stimulation (tRNS) was applied for the sham condition. tRNS was chosen for its broad frequency distribution, which limits any potential entrainment effects of the stimulation on somatosensory alpha activity[19]. Moreover, tACS and tRNS have been shown to result in a similar sensation. Fertonani et al. [14] who assessed sensations for different types of tES as reported by a large number of participants, found similar mild sensations for tACS and tRNS, both of a lower intensity than for tDCS. Where the average discomfort score for tDCS was 2.62, it was 1.57 for tACS and 1.25 for tRNS. Furthermore, Gundlach et al.[19], who applied somatosensory alpha tACS and tRNS in a similar manner as in the present study, did not identify any differences in tiredness and alertness for the tACS and tRNS sham condition. Although tiredness increased and alertness decreased over the time course of the session, there was no difference in change comparing tACS and tRNS. Furthermore, they did not identify a significant difference between the two conditions on whether or not the stimulation was perceived. In the present study, the tRNS was ramped up over a period of 10s at the onset of the experimental task, followed by 10s of tRNS, and finally ramped down again over a period of 10s adding up to a total period of 30s of sham stimulation.

Measurements

Pain experience

To quantify pain experience, participants received two 11-point numerical rating scales (NRSs) on the computer screen after each stimulation (ranging from 0-10) to measure perceived intensity and unpleasantness (0 = not at all intense/unpleasant, 10 = extremely intense/unpleasant). They were asked to rate their experience by typing a number using the keyboard.

Fear of Pain Questionnaire – Short Form

The Fear of Pain Questionnaire – Short Form (FPQ-SF) is a nine-item, 5-point rating scale based on the 30-item Fear of Pain Questionnaire (FPQ-III)[33], with items reflecting three categories of pain/painful situations: severe pain, minor pain, and medical pain. The FPQ-III is a well-validated questionnaire appropriate to use in both clinical and non-clinical populations[1,33,43]. Further validation of the FPQ-SF specifically demonstrated good internal consistency values ranging from .83-.87 for the FPQ-SF, and the FPQ-SF was highly correlated with the 30-item FPQ-III with r-values ranging from .94 to .97[44]. Participants were asked to rate how fearful they were (or expected they would be) of experiencing the pain associated with the painful experience described in each item, such as 'getting a paper-cut on your finger' and 'breaking your arm', on a 5-point scale ranging from 1-5, resulting in a total score ranging from 9-45 points, with a higher score indicating higher levels of fear of pain. The total score was used for statistical analysis.

Pain Catastrophizing Scale

The Pain Catastrophizing Scale[54] (PCS) contains 13 items. The items reflect three dimensions of pain catastrophizing: rumination, magnification, and helplessness. The PCS is a well-validated questionnaire, appropriate to be used in

both clinical and non-clinical populations[41,42,54]. Participants are asked to rate how much they experience the thoughts or feelings described in the items when they experience pain, such as 'when I'm in pain I worry all the time about whether the pain will end' and 'when I'm in pain I keep thinking about how much it hurts', on a 5-point rating scale ranging from 0-4, resulting in a total score ranging from 0-52 points. The total score was used for statistical analysis.

Procedure

The study consisted of two sessions, carried out around the same time of day and with at least one week between sessions to avoid any carry-over effects of the tACS. The experiment contained four different stimulation blocks: (1) alpha tACS and certain expectation; (2) alpha tACS and uncertain expectation; (3) sham and certain expectation, and (4) sham and uncertain expectation. Each session contained one block of alpha tACS and one block of sham stimulation, one of which was combined with certain and the other with uncertain expectation. Order of alpha tACS and sham was counterbalanced over the two sessions per participant: if the participants received alpha tACS first in the first session, they received sham first in the second session, and vice versa. The order of certain and uncertain expectation was kept the same for each individual participant over the two sessions, but was counterbalanced between participants: half of the participants started with the certain condition, the other half started with the uncertain condition (Fig.1). Participants were not made aware of the two different stimulation conditions (alpha tACS and sham) during the experiment but were debriefed after completion of the study.

For each session, the same experimental procedure was applied. At the start of each session the ramping procedure was carried out to identify the three individual

levels of pressure intensity. Following the tACS set-up, the participants carried out the pressure pain task, including one block of alpha tACS and one block of sham stimulation. Each block contained 72 trials (24 trials for each of the three pressure stimulus intensities). Every trial started with the presentation of a fixation cross (with a jittered duration of 750-1000 ms) followed by a visual cue (with a jittered duration of 2000-2750 ms). The visual cue was followed by pressure stimulation at one of three intensities (non-painful, pain threshold, and moderately painful). After pressure stimulation, the participants were asked to rate perceived intensity and unpleasantness using two 11-point NRSs. Participants received regular short breaks throughout the experiment. Each block was preceded by a short practice to familiarize the participant with the task in general and the function of the visual cues to induce a certain or uncertain expectation. Total duration of the experimental task was variable, depending on the time individual participants took to rate intensity and unpleasantness and duration of breaks, but was between 15 to 20 minutes for each block, adding up to 30-40 minutes total duration for the experiment.

Statistical analysis

Statistical analysis was carried out using SPSS version 21 (IMB Corp., Armonk, NY). Perceived pain intensity and unpleasantness tend to be highly correlated[59], as was the case for the intensity and unpleasantness ratings in the present study. When pain intensity was certain, a significant positive correlation between intensity and unpleasantness ratings was found for each pressure stimulus intensity, with r-values ranging from .60-.92 and p-values ranging from .000-.003. When pain intensity was uncertain similar significant positive correlations were found, with r-values ranging from .69-.95 and p-values all < .001. Therefore, to

investigate the effect of somatosensory alpha tACS on pain experience a repeated measures MANOVA was calculated with the within-subject factors stimulation (alpha tACS, sham), expectation (certain, uncertain) and pressure stimulus intensity (non-painful, pain threshold, moderately painful) and the dependent variables intensity and unpleasantness ratings. The significance level was set at $p < .05$. The Pillai's Trace outcome was used as the test statistic, as recommended by Olson[40] and O'Brien and Kaiser[39]. In the case of a significant effect, this was followed up by two 2x2x3 repeated measures ANOVAs with the within-subject factors stimulation (alpha tACS, sham), expectation (certain, uncertain) and pressure stimulus intensity (non-painful, pain threshold, moderately painful), one for the intensity ratings and one for the unpleasantness ratings. In the case of a violation of sphericity the Greenhouse-Geisser corrected outcomes were used. Finally, in case of significant effects in the ANOVAs, post-hoc repeated measures t-tests were carried out. To correct for multiple comparisons, the Bonferroni correction was applied.

To determine whether there was a significant change in intensity/unpleasantness rating as a result of alpha tACS Pearson correlations were calculated to investigate the relationship between change in pain experience for alpha tACS compared to sham (sham intensity/unpleasantness rating – alpha tACS intensity/unpleasantness rating) and fear of pain/pain catastrophizing. The Bonferroni correction was again applied.

Results

Alpha tACS and pain experience

The repeated measures MANOVA demonstrated a significant main effect of stimulus intensity ($F_{4,88} = 32.65$; $p < .001$; Partial $Eta^2 = .60$) but not of stimulation

($F_{2,21}$ = 2.07; p = .15; Partial Eta^2 = .17). However, a significant three-way interaction between stimulation (sham, alpha tACS), expectation (certain, uncertain), and stimulus intensity (non-painful, pain threshold, moderately painful) was present ($F_{4,88}$ = 2.94; p = .025; Partial Eta^2 = .12). Furthermore, a significant two-way interaction between stimulation (sham, alpha tACS) and stimulus intensity (non-painful, pain threshold, moderately painful) was present ($F_{4,88}$ = 3.27; p = .015; Partial Eta^2 = .13).

The two repeated measures ANOVA's for the intensity and unpleasantness ratings separately demonstrated a significant main effect of stimulation (sham, alpha tACS) on unpleasantness ratings ($F_{1,22}$ = 4.35; p = .049; Partial Eta^2 = .17), with an overall average unpleasantness rating (mean ± SD) of 3.30 ± 0.73 for the alpha tACS and 3.42 ± 0.75 for the sham condition. However, this did not survive correction for multiple comparisons at a significance level of .025. No significant main effect of tACS was present for the intensity ratings ($F_{1,22}$ = 2.31; p = .14; Partial Eta^2 = .095). However, a significant three-way interaction between stimulation (sham, alpha tACS), expectation (certain, uncertain), and stimulus intensity (non-painful, pain threshold, moderately painful) was found for the intensity ratings ($F_{2,44}$ = 4.50; p = .017; Partial Eta^2 = .17). In addition, a trend towards significance was present for the two-way interaction between stimulation and expectation for the intensity ratings ($F_{1,22}$ = 3.56; p = .073; Partial Eta^2 = .14). The same significant three-way interaction between stimulation (sham, alpha tACS), expectation (certain, uncertain), and stimulus intensity (non-painful, pain threshold, moderately painful) was found for the unpleasantness ratings ($F_{1,22}$ = 4.78; p = .040; Partial Eta^2 = .18). In addition, a significant two-way interaction between stimulation and expectation was present for the unpleasantness ratings ($F_{2,44}$ = 3.42; p = .042; Partial Eta^2 = .14).

However, these two interactions for the unpleasantness ratings did not survive correction for multiple comparisons at a significance level of .025.

Unpleasantness ratings. In the uncertain expectation condition, unpleasantness ratings (mean ± SD) for alpha tACS were consistently lower than ratings under the sham condition across all stimulus levels: 0.39 ± 0.58 and 0.44 ± 0.56 for non-painful pressure stimuli; 2.36 ± 1.33 and 3.07 ± 1.28 for pain threshold pressure stimuli; and 6.33 ± 1.72 and 7.17 ± 1.36 for moderately painful pressure stimuli. This was not the case in the certain expectation condition where unpleasantness ratings for alpha tACS and sham respectively were: 0.28 ± 0.38 and 0.28 ± 0.37 for non-painful pressure stimuli; 3.15 ± 0.88 and 2.66 ± 1.25 for pain threshold pressure stimuli; and 7.29 ± 1.44 and 6.92 ± 1.30 for moderately painful pressure stimuli.

Post-hoc paired-samples t-tests further supported that unpleasantness ratings were significantly lower during alpha tACS compared to sham only in the uncertain expectation condition and only for the pain threshold and moderately painful pressure stimuli. For the pain threshold pressure stimuli, unpleasantness ratings were 0.71 lower during alpha tACS (t_{22} = -2.34, p = .029), and for the moderately painful pressure stimuli unpleasantness ratings were 0.84 lower during alpha tACS (t_{22} = -2.65, p = .015) (Fig. 2). However, these did not survive correction for multiple comparisons at a significance level of .008. Nonetheless, calculation of the repeated measures Cohen's d effect sizes did demonstrate an effect of moderate strength, with an effect size of 0.49 for the pain threshold stimuli and an effect size of 0.55 for the moderately painful stimuli. For the non-painful pressure stimuli, no significant reduction of unpleasantness ratings as a result of alpha tACS was found (t_{22}= -0.43,

p = .67). In the certain condition, no significant difference in reported pain unpleasantness between alpha tACS and sham was found for any of the three pressure stimulus intensities (non-painful pressure stimuli, t_{22} = 0.135, p = .89; pain threshold pressure stimuli, t_{22} = 1.86, p = .073; and moderately painful pressure stimuli, t_{22} = 1.20, p = .24).

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Figure 2

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Intensity ratings. For the intensity ratings, a similar pattern of effects for tACS was found. In the uncertain expectation condition average intensity ratings for alpha tACS and sham respectively, were (mean ± SD): 0.92 ± 0.62 and 0.88 ± 0.50 for non-painful pressure stimuli; 3.19 ± 1.14 and 3.75 ± 1.08 for pain threshold pressure stimuli; and 6.74 ± 1.39 and 7.41 ± 1.09 for moderately painful pressure stimuli. In the certain expectation condition, average intensity ratings for alpha tACS and sham respectively were: 0.66 ± 0.44 and 0.77 ± 0.49 for non-painful pressure stimuli; 3.67 ± 0.82 and 3.40 ± 1.08 for pain threshold pressure stimuli; and 7.63 ± 1.14 and 7.19 ± 1.08 for moderately painful pressure stimuli.

Post hoc paired-samples t-tests further supported that intensity ratings were significantly lower during alpha tACS compared to sham only in the uncertain expectation condition and only for the pain threshold and moderately painful pressure stimuli. Intensity ratings were 0.56 lower during alpha tACS for the pain threshold pressure stimuli (t_{22} = -2.18, p = .040) and 0.67 lower for the moderately painful pressure stimuli (t_{22} = -2.73, p = .012) (Fig. 3). However, this did not survive

correction for multiple comparisons at a significance level of .008. Nonetheless, calculation of the repeated measures Cohen's d effect sizes did demonstrate an effect of moderate strength, with an effect size of 0.45 for the pain threshold stimuli and an effect size of 0.48 for the moderately painful stimuli. No significant reduction for alpha tACS was found for the non-painful pressure stimuli (t_{22} = 0.40, p = .69). In the certain condition, no significant difference in intensity ratings for alpha tACS compared to sham stimulation was found for any of the three pressure stimulus intensities (non-painful pressure stimuli, t_{22} = -1.05, p = .31; pain threshold pressure stimuli, t_{22} = 1.08, p = .29; and moderately painful pressure stimuli, t_{22} = 1.60, p = .12).

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Figure 3

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Correlation analysis

Pearson correlations between the change in intensity rating (sham rating – alpha tACS rating) and the FPQ-SF total score and the PCS total score were calculated (two-tailed significance), only for the difference between sham and alpha tACS in the uncertain condition and only for the two painful pressure intensities. The Bonferroni corrected level of significance for these tests was .0125 (as four hypotheses were tested for the intensity ratings: 2 (pressure stimulus intensity: pain threshold, moderately painful) x 2 (questionnaires: fear of pain, pain catastrophizing). The same correlation analysis was carried out for the unpleasantness ratings.

Exploring the relationship between alpha tACS and fear of pain. No significant relationship between fear of pain and the reduction in pain experience as a result of somatosensory alpha tACS was found. The reduction in intensity ratings for alpha tACS compared to sham was not significantly correlated with fear of pain (change in intensity ratings for pain threshold stimuli and fear of pain: $r = -.11$, $p = .66$; change in intensity ratings for moderately painful stimuli and fear of pain: $r = -.19$, $p = .45$). The reduction in unpleasantness ratings as a result of somatosensory alpha tACS was not significantly correlated with fear of pain (change in unpleasantness ratings for pain threshold stimuli and fear of pain: $r = -.20$, $p = .40$; change in unpleasantness ratings for moderately painful stimuli and fear of pain: $r = -.25$, $p = .30$).

Exploring the relationship between alpha tACS and pain catastrophizing. Pain catastrophizing was significantly positively correlated to the reduction in reported pain intensity for alpha tACS compared to sham (sham rating – alpha tACS rating), for the moderately painful pressure stimuli ($r = .47$, $p = .026$). However, this did not survive correction for multiple comparisons at a significance level of .0125. No significant relationship between pain catastrophizing and the reduction in reported pain intensity was found for pain threshold pressure stimuli ($r = .16$, $p = .47$). There was no significant correlation between pain catastrophizing and the reduction in reported unpleasantness for either pain threshold pressure stimuli ($r = .15$, $p = .51$) or moderately painful stimuli ($r = .34$, $p = .13$).

Carry-over effects

The four different stimulation blocks (alpha tACS and certain expectation, alpha tACS and uncertain expectation, sham and certain expectation, and sham and

uncertain expectation) were delivered over two sessions with at least a week between sessions. Each session contained one block of alpha tACS and one block of sham stimulation, one of which was combined with certain and the other with uncertain expectation. The order of alpha tACS and sham was counterbalanced over the two sessions; each participant received alpha tACS first in one session, and sham stimulation first in the other session. Therefore, half of the time the sham block was applied after the alpha tACS block with a short break of about 5 minutes in-between. To examine whether a carry-over effect from the alpha tACS to the sham block was present further analysis was carried out.

T-tests comparing intensity ratings during sham stimulation for participants that had the sham stimulation before the alpha tACS and participants that had the sham stimulation after the alpha tACS did not demonstrate a significant difference in intensity ratings. When pain intensity was certain, no significant difference in intensity ratings was found for any of the pressure stimulus intensities: non-painful stimuli, $t_{21} = -0.18$, $p = .86$; pain threshold stimuli, $t_{21} = 0.91$, $p = .37$; and moderately painful stimuli, $t_{21} = 0.80$, $p = .43$. When pain intensity was uncertain, no significant difference in intensity ratings was found either: non-painful stimuli, $t_{21} = -1.18$, $p = .25$, pain threshold stimuli: $t_{21} = -1.29$, $p = .21$, and moderately painful stimuli: $t_{21} = -1.27$, $p = .22$.

T-tests comparing unpleasantness ratings during sham stimulation for participants that had the sham stimulation before the alpha tACS and participants that had the sham stimulation after the alpha tACS also did not demonstrate a significant difference in unpleasantness ratings. When pain intensity was certain, no significant difference in unpleasantness ratings was present for any of the pressure stimulus intensities: non-painful stimuli, $t_{21} = -0.77$, $p = .45$; pain threshold stimuli, t_{21}

= 0.84, p = .41; moderately painful stimuli, t_{21} = 0.88, p = .39. No significant difference was present when pain intensity was uncertain either: non-painful stimuli, $t_{16.18}$ = -1.40, p = .18; pain threshold stimuli, t_{21} = -1.33, p = .20; moderately painful stimuli, t_{21} = -0.75, p = .46.

Discussion

This study explored the effects of alpha tACS applied over the somatosensory cortex on the experience of pain. As hypothesized, pain experience was significantly lower during alpha tACS compared to sham stimulation. However, this was only the case when participants were uncertain rather than certain about the intensity of an upcoming pain stimulus. This study is the first to indicate an effect of somatosensory alpha tACS on pain experience, particularly in a state of uncertainty. This suggests that interventions targeting somatosensory alpha activity may be a promising approach to reduce pain, but that a person's expectations about pain intensity must also be taken into account.

Thus far, evidence for a relationship between somatosensory alpha activity and pain experience was primarily based on a negative correlation between pre-stimulus/resting-state alpha activity and pain experience[2,38,58]. This study offers a first behavioural exploration of the potential of modulating somatosensory alpha activity to reduce pain. In line with studies demonstrating an increase of alpha for alpha tACS applied over posterior-occipital regions[20,28,37,61,68], it was expected that somatosensory alpha tACS would result in an increase of somatosensory alpha. The present finding of lower pain experience during tACS compared to sham stimulation corresponds with what was expected based on the negative correlation between somatosensory alpha and pain experience. Furthermore, it provides an initial

behavioural indication of a causal relationship between somatosensory alpha activity and pain experience. However, this is complicated by the study's finding on the impact of uncertainty about stimulus intensity.

Previous studies have suggested an effect of uncertainty on alpha activity before pain onset[16,25]. The present study offers a first indication that uncertainty also influences the effects of somatosensory alpha tACS on pain experience. However, it remains unclear why somatosensory alpha tACS led to lower pain experience only in an uncertain setting. Perhaps the effects of alpha tACS depend on the state of the targeted neural region. In the visual domain a significant increase of occipital alpha power was found only when endogenous alpha activity was low (eyes open) but not when it was high (eyes closed)[37]. Similarly, phase synchronization of occipital alpha activity with alpha tACS was found only when endogenous alpha activity was low[52]. This suggests that the effects of alpha tACS are not necessarily static but depend on the state of the targeted neural network.

Although a state of uncertainty cannot be compared directly to a state of high or low occipital alpha activity due to having the eyes open or closed, it is possible that uncertainty compared to certainty about pain intensity resulted in a different endogenous somatosensory alpha state[16,25]. Uncertainty about pain intensity is considered to reflect higher threat value[10]. A recent study demonstrated that the amount of threat perceived during the anticipation of pain affected pre-stimulus somatosensory alpha activity[24]. Viewing a needle (threatening) compared to a cotton bud approaching the hand (non-threatening), resulted in a significantly stronger reduction of pre-stimulus alpha activity. This suggests that a setting of higher threat, e.g., uncertainty about pain intensity, might result in a different endogenous alpha state. Further research on the different neural states related to certain and uncertain

pain intensity could assist a better understanding of how somatosensory alpha tACS affects pain experience.

A better understanding of the conditions that lead to lower pain during somatosensory alpha tACS is critical for its clinical application. Interventions targeting oscillatory neural activity, such as tACS, have been proposed for the treatment of pain[27] and the present findings provide initial evidence to support this, albeit in an experimental pain setting. However, the effect of somatosensory alpha tACS might not generalize to all settings, but depends on uncertainty about pain. With uncertainty related to higher reported anxiety[46] and a higher threat value[10], somatosensory alpha tACS might be most suitable in settings where patients experience more uncertainty, anxiety, or threat of pain. Notably, these settings tend to be related to increased pain and pain-related distress. For instance, viewing a needle approach the hand whilst anticipating pain, resulted in not only a stronger reduction of pre-stimulus alpha activity, but also significantly higher unpleasantness ratings[24]. Also, state anxiety one day before surgery was found to correlate significantly with post-operative reported pain intensity[18]. A better understanding of how clinical context and patients' characteristics relate to the effectiveness of alpha tACS to reduce pain could optimize individual outcomes[32].

The present study is one of the few studies investigating the effects of somatosensory alpha tACS on somatosensory perception in general. It expands the findings from Feurra et al.[15] and Gundlach et al.[19] of somatosensory alpha tACS inducing a tactile sensation[15], and an increase of perception thresholds for near-threshold tactile stimuli at a certain phase angle of the tACS signal (i.e., a phase-dependent effect on tactile perception)[19]. To date, no tonic effect of somatosensory

alpha tACS on non-painful somatosensory perception has been demonstrated. The present study is the first to find an effect of somatosensory alpha tACS on painful somatosensory perception. However, similar to Gundlach et al.[19], no change in non-painful somatosensory perception was found averaged over all trials (not sorted by phase). This suggests that the effect of somatosensory alpha tACS on somatosensory perception might be specific to the painful domain, and that the involvement of somatosensory alpha activity might be different for painful and non-painful somatosensory perception.

Limitations

In this study the application of alpha tACS and sham stimulation was counterbalanced: for each of the two sessions half of the participants received alpha tACS and half sham first. However, in the visual domain an aftereffect of occipital alpha tACS has been demonstrated. When alpha tACS was applied for at least 10 minutes a significant increase of alpha remained present for at least 30 minutes[37] up to 70 minutes after tACS offset[28]. Thus, a carry-over effect might be present when sham is applied after tACS. Although there was a short break between tACS and sham in this study, the duration of aftereffects as found for occipital alpha tACS suggests that a carry-over effect might still be present. However, we did not find any evidence for this. Nonetheless, it remains critical to keep in mind the potential for carry-over effects in the design of future studies.

As the work on somatosensory alpha tACS is still in its infancy, and this study is the first to focus on pain specifically, many questions remain to be answered. Although it was hypothesized that a reduction of perceived pain by somatosensory alpha tACS would take place via an increase of somatosensory alpha power, this

study did not include a neurophysiological measurement to confirm this. Assessment of neurophysiological changes as a result of somatosensory alpha tACS is an important next step in understanding the effects of tACS on pain experience. Another question, especially relevant for the clinical application of somatosensory alpha tACS, is for how long does the reduction in pain last following somatosensory alpha tACS? In the visual domain, an aftereffect of occipital alpha tACS has been demonstrated. Investigating aftereffects of somatosensory alpha tACS could be a useful step in exploring the potential of somatosensory alpha tACS as pain treatment.

Finally, we should be careful to assign the effect of somatosensory alpha tACS on pain experience to a change in somatosensory alpha activity alone, and make note of the possibility that it was due to an increase in alpha in the somatosensory cortex and adjacent regions. However, for the practical application of somatosensory alpha tACS to reduce pain, a more widespread effect of somatosensory alpha tACS is not necessarily a limitation. Pain experience does not emerge from a single neural region, but is the result of processing in a widespread neural network[34]. Neural oscillatory activity, including alpha activity, is thought to support the communication within this functional neural network[4,17]. Battleday et al.[5] hypothesized that the effects of tACS on functions arising from distributed neural networks might be due specifically to a more widespread effect of tACS. As tACS changes oscillatory activity in one region this affects the communication of that region with its wider neural network, modulating the effectiveness of information processing in the network. Thus, an effect of somatosensory alpha tACS beyond the somatosensory cortex may not be a limitation when we are concerned with achieving a reduction in pain, but instead might prove to be beneficial.

Summary

This study is the first to demonstrate an effect of somatosensory alpha tACS on pain experience. Pain experience was significantly lower during alpha tACS compared to sham stimulation. This provides some initial indication of a causal relationship between somatosensory alpha activity and pain experience. Furthermore, this study suggested an influence of cognitive-emotional state on the effectiveness of alpha tACS, as pain experience was only lower when participants were in a state of uncertainty about pain intensity. This may have implications for the application of tACS to reduce pain in a clinical setting. Finally, as one of the few studies investigating the effects of somatosensory alpha tACS this study also contributes to the general field of alpha tACS, expanding its application from the visual and motor domain to the somatosensory domain.

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Figure Legends

Figure 1. (A) Overview of experimental procedure. The study included four conditions in total, delivered in four blocks: alpha tACS – uncertain, alpha tACS – certain, sham – uncertain, and sham – certain. These four stimulation blocks were delivered over two sessions: one session with the blocks alpha tACS – uncertain and sham – certain, and one session with the blocks alpha tACS – certain and sham – uncertain. The order of stimulation conditions (alpha tACS, sham) was counterbalanced for each participant over the two sessions. The order of the certain and uncertain condition was the same for an individual participant over the two sessions. The order was counterbalanced between participants though, with half of the participants starting with certain expectation and the other half with uncertain expectation; (B) Illustration of the manipulation of expectation (certain or uncertain) using visual cues that were presented directly before the onset of each pressure stimulus.

Figure 2. Top: average unpleasantness ratings comparing alpha tACS to sham stimulation, for certain (left) and uncertain (right) expectation (N = 23). The error bars depict the standard error of the mean. P-values of post hoc t-tests comparing rating scores for tACS and sham are displayed for each pressure intensity and expectation condition (certain, uncertain), only for outcomes with $p < .05$. **Bottom:** scatterplots of the difference in unpleasantness rating for alpha tACS and sham stimulation (sham – alpha tACS) for certain (left) and uncertain expectation (right).

Figure 3. Top: average intensity ratings comparing alpha tACS to sham stimulation, for certain (left) and uncertain (right) expectation (N = 23). The error bars depict the

standard error of the mean. P-values of post hoc t-tests comparing rating scores for tACS and sham are displayed for each pressure intensity and expectation condition (certain, uncertain), only for outcomes with $p < .05$. **Bottom:** scatterplots of the difference in intensity rating for alpha tACS and sham stimulation (sham – alpha tACS) for certain (left) and uncertain expectation (right).

Figure 1

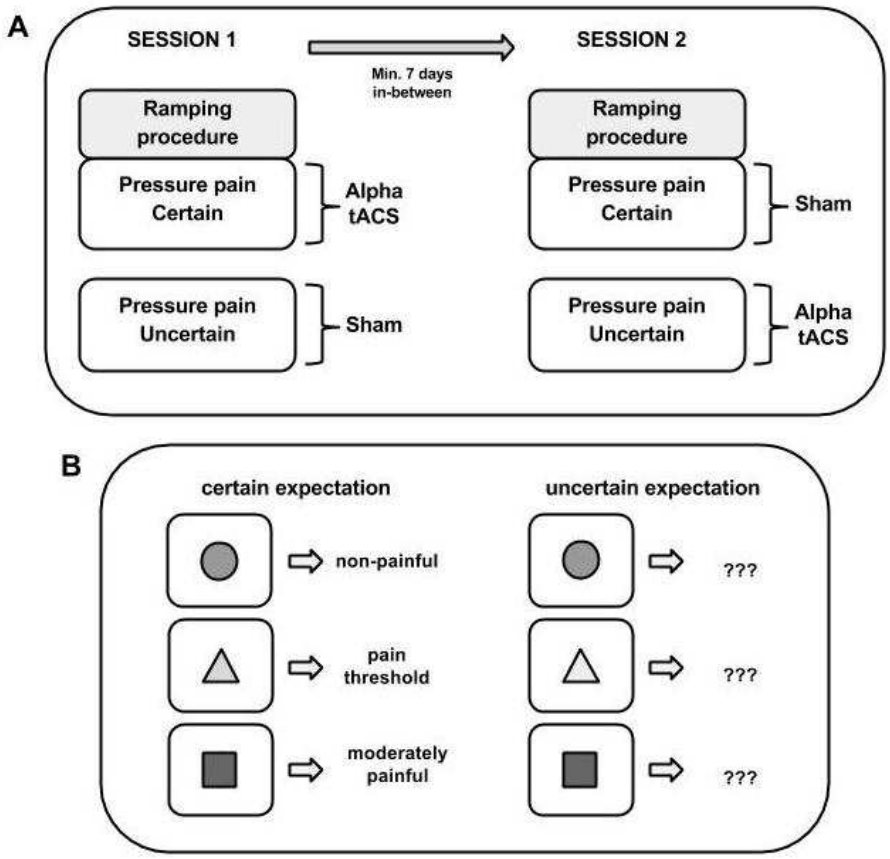

Figure 2

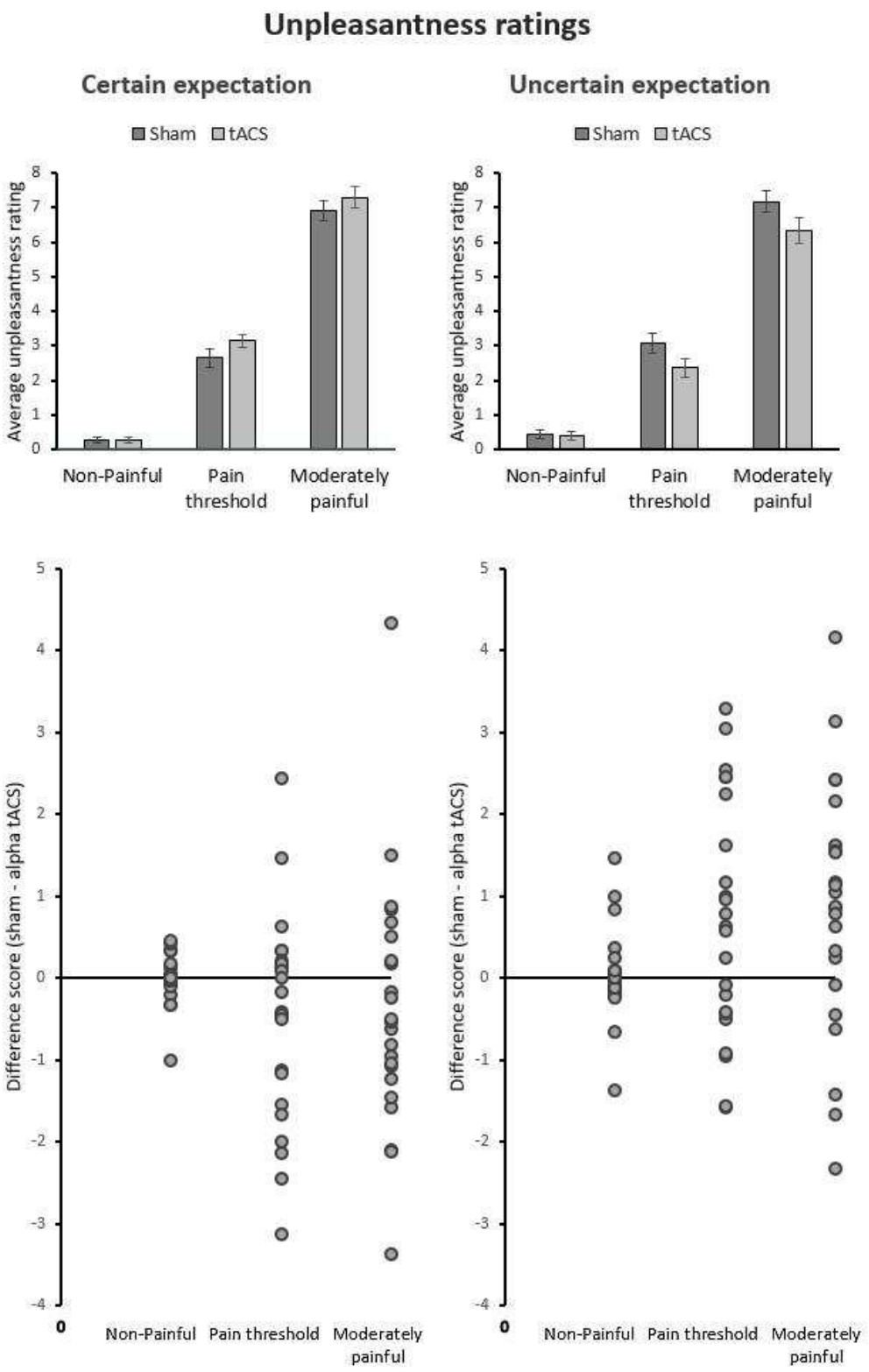

Figure 3