Clinical Neurophysiology 129 (2018) 1201–1208

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

The efficacy of transcranial random noise stimulation (tRNS) on mood may depend on individual differences including age and trait mood

Carys Evans, Michael J. Banissy, Rebecca A. Charlton *

Department of Psychology, Goldsmiths, University of London, UK

ARTICLE INFO

Article history:
Accepted 10 March 2018
Available online 31 March 2018

Keywords:
Transcranial random noise stimulation
Brain stimulation
Aging
Cardiovascular risk
Depression

HIGHLIGHTS

- At a group level, transcranial random noise stimulation (tRNS) over bilateral dorsolateral prefrontal cortex did not significantly improve mood across participants.
- Individual differences in age and trait mood affect the direction of mood change in response to tRNS.
- Mood change was comparable in older adults with and without cardiovascular risk factors.

ABSTRACT

Objectives: To assess whether changes in brain microstructures associated with ageing and presence of cardiovascular risk factors (CVRF) reduce the efficacy of transcranial electrical stimulation (tES) improving mood in euthymic older adults.

Methods: Using excitatory high-frequency transcranial random noise stimulation (tRNS) over bilateral dorsolateral prefrontal cortex, the effect on mood was assessed in euthymic young adults (YA), older adults (HOA) and older adults with CVRF (OVR). Active-tRNS or sham was applied over two sessions. Positive and Negative Affect Schedule and Warwick Edinburgh Mental Well-being Scale measured self-reported state mood before and after stimulation. Trait mood was also measured using the Geriatric Depression Scale.

Results: Response to tRNS seemed dependent on individual differences in age and trait mood. In HOA, more negative trait mood was associated with more positive mood change after tRNS. OVR showed a similar but reduced pattern of mood change to HOA. In YA, more positive trait mood was associated with greater positive mood change after tRNS.

Conclusions: Age and trait mood may be important factors when examining the efficacy of tES as an alternative treatment for depression.

Significance: Future studies should consider how response to tES is affected by individual differences.

1. Introduction

Major depressive disorder (MDD) is common among otherwise healthy older adults, occurring in more than 13% of individuals over 60 years old (Beekman et al., 1999). Despite this, less than a quarter of older adults with depression receive treatment (Roose and Schatzberg, 2005). Older adults diagnosed with MDD may be refractory to treatment, reluctant to start drug therapies and have residual cognitive difficulties even when depression symptoms abate (Alexopoulos, 2005; Barch et al., 2012). Beyond MDD, 15% of older adults are estimated to have sub-clinical levels of depression and persistent low mood (dysthymia) that impairs quality of life and is associated with poor cognitive performance (Barch et al., 2012). Given the ageing population and prevalence of dysthymia, alternate therapies for MDD and dysthymia is vital. Transcranial electrical stimulation (tES), a non-invasive method where a weak electrical current is applied to the head to excite or inhibit neural activity (Jorge and Robinson, 2011) may be an alternative to standard treatments. Preliminary evidence suggests that tES may improve mood in young adulthood but its efficacy among older adults has not been examined. This study will examine the effects of tES on mood in euthymic younger and older adults.

Studies exploring the effects of tES have predominantly used transcranial direct current stimulation (tDCS; tES where a direct

* Corresponding author at: Department of Psychology, Goldsmiths, University of London, New Cross, London SE14 6NW, UK.
E-mail address: r.charlton@gold.ac.uk (R.A. Charlton).

https://doi.org/10.1016/j.clinph.2018.03.012
1388-2457/

current is applied) and have demonstrated that tES applied to the dorsolateral prefrontal cortex (DLPFC) can improve mood in young adults with and without MDD (Boggio et al., 2008; Brunoni et al., 2014; Ferrucci et al., 2009). The left DLPFC is often targeted for active tES as it may be hypoactive in MDD (Grimm et al., 2008; Koenigs and Grafman, 2009). In young adults with MDD, tDCS of the left DLPFC resulted in reduced depression ratings (Boggio et al., 2008). Among adults with MDD (18–65 years), Brunoni and colleagues (Brunoni et al., 2014) demonstrated a reduction in depressive symptoms (immediately after treatment and at two-week follow-up) when bilateral DLPFC tDCS was applied while a working memory task was performed over 10 sessions. Positive effects of left DLPFC stimulation have been reported in healthy participants, where stimulation facilitated cognitive reappraisal (Feeser et al., 2014) and reduced self-reported emotional distress when viewing aversive stimuli (Boggio et al., 2009). TES has not yet been applied to elevate mood in older adults either with or without MDD.

Whilst tES shows promise, research suggests its effects on mood or cognition may vary depending on the individual. These findings warrant the need to assess whether the effects of tES may differ in late-life compared to young adulthood. Although tES has not yet been applied in a systematic fashion to effect mood in ageing, one case report has been identified. In a 92-year-old-patient with MDD, improved mood was demonstrated after 10 sessions of tDCS to the left DLPFC (Shiozawa et al., 2014a). Further studies have used a different brain stimulation technique, transcranial magnetic stimulation (TMS). TMS uses a rapidly changing magnetic field to temporarily modulate the function of the targeted cortical area (Pascual-Leone et al., 1999). High-frequency repetitive TMS (rTMS) to the left DLPFC can enhance excitability, resulting in improved mood in young adults (Jorge and Robinson, 2011) and older adults with vascular depression (Jorge et al., 2008). However other rTMS studies have shown an inconsistent or absence of any antidepressant effects (Manes et al., 2001; Mosimann et al., 2004) and the efficacy of tDCS has not been established. As such, while brain stimulation may be effective in treating depression, its role as an alternative therapy is yet to be established (Berlim et al., 2013; Slotema et al., 2010).

Differences across study findings corroborate the suggestion that the efficacy of tES may be partly dependent on individual differences within different populations. Further, whilst TMS has high spatial and temporal frequency, it is expensive and difficult to apply. In contrast tES produces lasting after-effects on behaviour, is safe, inexpensive and easy to apply (Kadosh, 2013; Nitsche and Paulus, 2011). When tDCS has been applied with older adults it has primarily been with the aim of improving cognition (Meinzer et al., 2013), where DLPFC stimulation has improved executive function (Berryhill and Jones, 2012; Zimerman and Hummel, 2010). Although the optimal stimulation protocol for improvement is not yet clear, these studies suggest that tES may be an effective intervention in ageing, and has potential as a therapeutic technique in late-life depression (Jorge and Robinson, 2011).

Though tDCS to target a specific site may be optimal for young adults where unilateral neural networks are well understood, it may be less effective for older adults where differences in functional networks have been observed (Cabeza, 2002). When young adults typically recruit unilateral brain regions to complete a task, older adults often demonstrate reduced task-specific hemispheric asymmetry and rely on bilateral activation (Cabeza, 2002; Zimerman and Hummel, 2010). This bilateral activity in older adults has been hypothesised to be compensatory, as it is associated with better task performance compared to older adults who demonstrate unilateral activation, and results in equivalent performance to young adults who show unilateral activity (Cabeza, 2002). These network changes have been linked to age-related differences in response to tDCS where, unlike younger adults, older adults have shown a reversed pattern of response, or behavioural effects after homologous regions in the contralateral hemisphere were stimulated (Ross et al., 2011; Zimerman and Hummel, 2010). Therefore unilateral tDCS stimulation may be less effective in older adults. Unlike tDCS, transcranial random noise stimulation (tRNS) is not constrained by current flow direction and provides excitation at both electrode sites (Terney et al., 2008), which may be more effective with older adults who rely on bilateral activity. Recent studies have also suggested that tRNS demonstrated stronger effects than tDCS including a case of MDD where greater symptom reduction was reported after tRNS compared to tDCS (Chan et al., 2012; Fertonani et al., 2011). Further, tRNS may provoke fewer cutaneous effects (e.g. itching sensation) than tDCS, making it appropriate for studies where participants receive both active and sham tES (Ambrus et al., 2010). This is particularly important in studies of self-reported mood where there is risk of placebo effects. The efficacy of high-frequency tRNS to modulate mood across the lifespan remains an important question that has not yet been explored.

Cardiovascular risk factors (CVRF) such as high-blood pressure or diabetes which lead to cardiovascular damage in the brain, are common in ageing (Kennedy and Raz, 2009; Knopman et al., 2011; Raz et al., 2007) and may also influence the efficacy of tES. CVRF have been shown to disrupt white matter microstructure that support neural networks involved in cognition and mood regulation (Alexopoulos, 2005; Taylor et al., 2013; Kennedy and Raz, 2009; Verdelho et al., 2007). Age-related disruption in white matter microstructure has been demonstrated throughout the brain but particularly in anterior regions including the DLPFC where degradation is associated with late-life depression (Bae et al., 2006; O'Sullivan et al., 2001). It is not yet clear whether cardiovascular damage to white matter may further influence the efficacy of tES or the spread of stimulation across the affected neural networks in older adults. Therefore the current study will also examine CVRF and its impact on response to tES.

In this study we examine the efficacy of tRNS applied bilaterally to the DLPFC (implicated in mood regulation by previous research) to improve mood in older euthymic adults with and without CVRF, and young adults. Participants received both active and sham tRNS using a double-blind design; presence of CVRF among older adults was measured. We hypothesised that: (1) tRNS may be as effective in older compared to younger euthymic adults and (2) that efficacy of tRNS among older adults would be associated with fewer CVRF. We also sought to explore whether individual differences in trait mood levels (i.e. long-term mood characteristics) influences response to tRNS.

2. Methods

2.1. Participants and procedure

Participants: recruitment was conducted through community outreach and local newspaper advertising. Exclusion criteria included any contraindications to tRNS (Rossi et al., 2009) and current or recent history of depression, presence of psychiatric or neurological conditions. These criteria minimised the variance in baseline cortical excitability introduced by psychological or psychiatric problems, which can moderate and potentially reverse the anticipated excitatory effect of tES (Krause and Cohen Kadosh, 2014). Furthermore, since the efficacy of tES has not yet been established, an initial study on euthymic individuals was deemed a necessary step prior to interventions with patients, which may have negative effects. Ten people were excluded from the study at initial screening (current/recent history of depression

n = 8; contraindication to tRNS n = 1; reason not given for ineligibility n = 1). Sixty older adults aged over 60 years (M_{age} = 67.33 ± 6.7, 25 male) and 30 younger adults (YA) aged 20–40 years (M_{age} = 26.37 ± 5.3, 14 male) participated. Older adults (OA) were divided into two groups, healthy older adults (HOA) and older adults with CVRF (OVR). OVR had a diagnosis of hypertension, diabetes, or had a high average blood pressure reading (>140 systolic and/or >90 diastolic) at the time of testing. A modified version of the Framingham Stroke Risk Profile excluding age as a risk factor (FSRP; Wolf et al., 1991) was recorded to quantify CVRF. See Table 1 for demographic information. All participants gave written informed consent and were given an honorarium of up to £40 for taking part. The study was approved by Goldsmiths University of London Ethics committee.

2.2. Assessment

Background Measures: depressive symptoms were measured using the Geriatric Depression Scale (GDS; Yesavage, 1988) in both sessions of the study; GDS scores quantified *trait* mood whereby a higher score indicated lower trait mood. The scale was administered to all participant groups as it has been shown to be appropriate for use with young adults (Weintraub et al., 2007). Whilst trait mood was expected to be stable, the GDS was measured in both sessions to rule out any anomalous changes in mood. The Mini-mental state exam (MMSE; Molloy et al., 1997) was used as a screen for cognitive impairment across participants (at risk <24); all participants scored above this cut-off (see Table 1). The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) was used to estimate full-scale IQ (FSIQ).

Experimental Measures: in both sessions, participants completed the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) and Warwick-Edinburgh Mental Well-being Scale (WEMWBS; Tennant et al., 2007) before and after stimulation (active-tRNS/sham). Participants completed each questionnaire in relation to how they felt at that moment in time to quantify current mood *state*. These scores were used to quantify mood change due to tRNS. Scores on the PANAS-negative affect were low and little variance was observed. Due to suspected floor effects, this measure was not used in the analysis. For both PANAS-positive affect and WEMWBS higher scores indicate more positive mood.

2.3. Transcranial random noise stimulation (tRNS)

After completing the mood questionnaires, stimulation was applied using a DC-Stimulator Plus device (neuroConn, Germany). During active-tRNS, 1 mA of high-frequency stimulation was applied for 10 min. The duration of after effects were unknown, yet based on previous research were anticipated to be shorter than the 60 min observed when targeting the motor cortex (Nitsche and Paulus, 2011). Two 5×5 cm (25 cm^2) rubber electrodes were encased in saline-soaked sponges and positioned bilaterally over the DLPFC (identified using F3 and F4 based on the 10-20 system as per previous studies (Boggio et al., 2008; Brunoni et al., 2014; Shiozawa et al., 2014b). Stimulation was ramped up and down for 15 s at the beginning and end of stimulation. During sham, the current was applied for 30 s after ramping up before switching off. Such a short duration of tRNS has been shown to have no effect on cortical excitability (Ambrus et al., 2010; Kadosh, 2013) and to be indistinguishable from active-tRNS (Ambrus et al., 2010; Kadosh, 2013).

2.4. Procedure

All participants attended two sessions where they received active-tRNS or sham stimulation using a double-blind procedure. Sessions were between 2 and 14 days apart (M = 5.9 days ± 4.2). Stimulation type (active-tRNS/sham) was randomised and counterbalanced across participants. In the first session participants were given a brief interview to assess the presence of any CVRF and completed the cognitive tests. Participants also identified two positive memories, one of which would be recalled and described to the researcher in each session. In both sessions, participants completed the GDS to describe trait mood followed by the pre-stimulation PANAS and WEMWBS describing state mood. During the first five minutes of stimulation participants sat quietly and for the remaining five minutes participants described one of the identified positive memories in order to induce a more positive mood. Immediately after stimulation, participants completed the post-stimulation PANAS and WEMWBS.

2.5. Data analysis

As presence of depression was an exclusion criterion for the study, GDS scores were reviewed. One YA was removed from the analyses having scored 23 (severe depression) on the GDS. Among the remaining participants a maximum of 15/30 was recorded on the GDS (criteria for mild depression score $\geq$10) with an average score of 4.13 (SD = 3.87). Grubbs' test (Grubbs, 1969) for outliers on Mood Change identified three participants (two HOA; one YA) as outliers who were removed from the analyses. As GDS scores were not normally distributed (Shapiro-Wilk$_{(86)}$ = .864, p < .001) they were converted into z scores for use in the analyses. This was expected due to our exclusion criteria. Group differences in demographic variables were analysed using ANOVA or Chi-Square as appropriate.

The effect of stimulation (active-tRNS/Sham) on mood state was assessed using a Mood Change difference score calculated by deducting the total score for positive affect/well-being prior to stimulation from the total score after stimulation: Mood Change = Mood score$_{Post\ Stimulation}$ − Mood score$_{Pre\ Stimulation}$. A positive score indicated an improvement in mood state after stimulation

Table 1
Demographics for each participant group, mean (standard deviation).

Demographics	YA (n = 28)	HOA (n = 28)	OVR (n = 30)	ANOVA	Group differences
Sex (M:F)	13:15	11:17	13:17	$F_{(2,83)}$ = .142, p = .868	–
Age	26.68 (5.4)	67.43 (7.0)	66.90 (6.6)	$F_{(2,83)}$ = 382.668, p < .001***	YA < HOA/OVR
Education level[a]	4.50 (1.2)	4.36 (1.8)	3.77 (1.9)	$F_{(2,83)}$ = 1.590, p = .210	–
Trait Mood (GDS)	5.32 (3.5)	2.71 (3.2)	4.33 (4.4)	$F_{(2,83)}$ = 3.437, p = .037*	YA < HOA
MMSE	29.57 (0.7)	29.14 (1.3)	29.17 (1.0)	$F_{(2,83)}$ = 1.539, p = .221	–
FSRP(%)$_{No\ Age}$	1.79 (1.3)	1.83 (1.0)	4.19 (2.3)	$F_{(2,83)}$ = 20.502, p < 001***	OVR > HOA/YA
WTAR FSIQ	109.89 (6.6)	111.50 (5.8)	109.60 (6.9)	$F_{(2,83)}$ = .710, p = .495	–

* p < .05.
*** p < .001. –: comparable between groups; <: significant difference between adjacent groups.
[a] Education level coding: 0 = no qualification; 1 = GCSE/NVQ (16 yrs); 2 = City & Guilds or other post 16 qualification; 3 = A Level/BTEC/Access course; 4 = Diploma/HND; 5 = Degree; 6 = Masters; 7 = PhD.

and a negative score indicated a reduction in mood state after stimulation. A repeated-measures ANOVA assessed Mood Change across the whole participant sample across Stimulation conditions (active-tRNS/Sham). Mixed model ANOVAs explored whether Mood Change differed depending on Stimulation and Age (YA/OA), and depending on Stimulation and Age/CVRF (YA/HOA/OVR). A Bonferonni correction was applied to post hoc analyses to correct for multiple comparisons.

To assess the effect of individual differences on response to stimulation, separate multiple regression analyses were conducted for PANAS-Positive and WEMWBS Mood Change scores. These were performed for each sham and active-tRNS sessions using the enter method to examine the relationship between Mood Change and four potential predictors: Trait Mood (GDS), Age, FSRP (%), and the interaction term Group × GDS score (YA × GDS; HOA × GDS; OVR × GDS).

3. Results

3.1. Demographics & GDS scores between sessions

3.1.1. Group differences

Participant groups were comparable in terms of sex, education level, and cognition (MMSE, FSIQ). As expected, YA were significantly younger than the HOA and OVR. Similarly, OVR demonstrated significantly higher CVRF than YA and HOA when quantified with the FSRP. YA had significantly lower trait mood on the GDS compared HOA but not OVR participants, see Table 1. GDS scores measuring trait mood did not differ significantly between sessions for the whole sample ($t_{(85)} = -1.057$, $p = .293$) or each group; HOA ($t_{(27)} = -.957$, $p = .347$), OVR ($t_{(29)} = -1.092$, $p = .284$), or YA ($t_{(27)} = .429$, $p = .671$). The relationship between GDS score and baseline mood (positive affect and well-being scores pre-stimulation) was also consistent across all groups in both active-tRNS and sham sessions; HOA, OVR, and YAs showed a significant negative correlation between GDS and baseline well-being, and non-significant negative correlation between GDS and baseline positive affect (data not shown).

3.2. Effect of active-tRNS/sham on state mood

ANOVAs assessed whether tRNS improved positive affect/well-being across the whole sample, and whether the effect of tRNS on state mood differed depending on age (YA/OA) or presence of cardiovascular risk factors (YA/HOA/OVR).

3.2.1. PANAS-positive affect ANOVAs

Whole sample: repeated-measures ANOVA confirmed a non-significant main effect of Stimulation (active-tRNS/sham) indicating that change in positive affect was consistent between active-tRNS (M = 1.29 ± 4.35) and sham (M = .85 ± 4.06) conditions ($F_{(1,85)} = .611$, $p = .437$, $\eta_p^2 = .007$).

YA and OA: mixed model ANOVA demonstrated non-significant main effects for Stimulation ($F_{(1,84)} = .380$, $p = .539$, $\eta_p^2 = .005$), Age ($F_{(1,84)} = .443$, $p = .507$, $\eta_p^2 = .005$), and interaction Stimulation × Age ($F_{(1,84)} = .104$, $p = .748$, $\eta_p^2 = .001$) indicating that Mood Change was comparable for both YA and OA in both active-tRNS and sham conditions.

YA, HOA, and OVR: non-significant main effects for Stimulation ($F_{(1,35)} = .567$, $p = .453$, $\eta_p^2 = .007$), Age/CVRF group ($F_{(2,83)} = .234$, $p = .792$, $\eta_p^2 = .006$), and interaction Stimulation × Age/CVRF ($F_{(2,83)} = .199$, $p = .820$, $\eta_p^2 = .005$) confirmed Mood Change did not differ depending on stimulation condition, age or presence of cardiovascular risk factors.

3.2.2. WEMWBS ANOVAs

Whole sample: change in well-being was comparable between active-tRNS (M = 1.40 ± 4.08) and sham (M = 1.44 ± 3.52) conditions ($F_{(1,85)} = .008$, $p = .927$, $\eta_p^2 < .001$) across all participants.

YA and OA: non-significant main effects of Stimulation ($F_{(1,84)} = .017$, $p = .896$, $\eta_p^2 < .001$), Age ($F_{(1,84)} = .446$, $p = .506$, $\eta_p^2 = .005$), and interaction Stimulation × Age ($F_{(1,84)} = .017$, $p = .896$, $\eta_p^2 < .001$) confirmed that well-being did not significantly differ depending on stimulation condition or age.

YA, HOA, and OVR: Mood Change did not differ depending on the age of the participants or presence of cardiovascular risk factors as demonstrated by non-significant main effects of Stimulation ($F_{(1,83)} = .005$, $p = .943$, $\eta_p^2 < .001$), Age/CVRF ($F_{(2,83)} = .237$, $p = .790$, $\eta_p^2 = .006$), and interaction Stimulation × Age/CVRF ($F_{(2,83)} = .309$, $p = .735$, $\eta_p^2 = .007$).

3.3. Effect of individual differences on mood change

Although non-significant effects of tRNS on Mood Change was observed at a group level, regression analyses assessed whether individual differences influenced participants response to tRNS. These were performed for each sham and active-tRNS session using the predictors age, trait mood (GDS), cardiovascular risk (FSRP%), and interaction terms YA × GDS, HOA × GDS, and OVR × GDS.

3.3.1. PANAS-positive affect regressions

Active-tRNS: the model significantly explained 14.4% of the variance in Mood Change ($F_{(5,80)} = 2.702$, $p = .026$, $R^2 = .144$, $R^2_{Adjusted} = .091$) with the interaction terms YA × GDS ($\beta = -2.450$, $t_{(80)} = -2.596$, $p = .011$) and HOA × GDS ($\beta = 2.129$, $t_{(80)} = 2.184$, $p = .032$) contributing significantly to the model. In YA, mood reduced by 2.45 points for each point on the GDS; the lower trait mood – the greater negative change in mood state after active-tRNS. In HOA, mood increased by 2.18 with each point on the GDS; the lower trait mood – the more positive change in mood state after active-tRNS. Age, GDS, FSRP, and OVR × GDS did not contribute significantly to the model ($p \geq .219$). Fig. 1 indicates that both HOA and OVR demonstrate a similar association between Mood Change after tRNS and GDS.

Sham: the model did not significantly explain any variance in Mood Change after sham ($F_{(5,80)} = .738$, $p = .597$, $R^2 = .044$, $R^2_{Adjusted} = -.016$).

Including baseline state mood: to confirm that baseline state mood was not driving the results, positive affect score pre-stimulation was included as an additional predictor. Results confirmed that baseline state mood did not significantly contribute to either model. During active-tRNS, the model significantly explained 14.4% of the variance in Mood Change ($F_{(6,79)} = 2.275$, $p = .045$, $R^2 = .147$, $R^2_{Adjusted} = .083$). During sham, the model did not significantly explain variance in Mood Change ($F_{(6,79)} = .644$, $p = .695$, $R^2 = .047$, $R^2_{Adjusted} = -.026$).

3.3.2. WEMWBS regressions

Active-tRNS: the model significantly explained 16.8% of the variance in well-being change ($F_{(5,80)} = 3.241$, $p = .010$, $R^2 = .168$, $R^2_{Adjusted} = .116$); the interaction term YA × GDS ($\beta = -2.941$, $t_{(80)} = -3.370$, $p = .001$) contributed to the model. In YA, mood reduced by 2.94 points for each point on the GDS. The lower trait mood scores, the greater the negative change in mood state after tRNS. Age, GDS, FSRP, HOA × GDS, and OVR × GDS did not contribute significantly to the model ($p \geq .194$).

Sham: Variance in Mood Change after sham stimulation was not significantly explained by the model ($F_{(5,80)} = 1.434$, $p = .221$, $R^2 = .082$, $R^2_{Adjusted} = .025$).

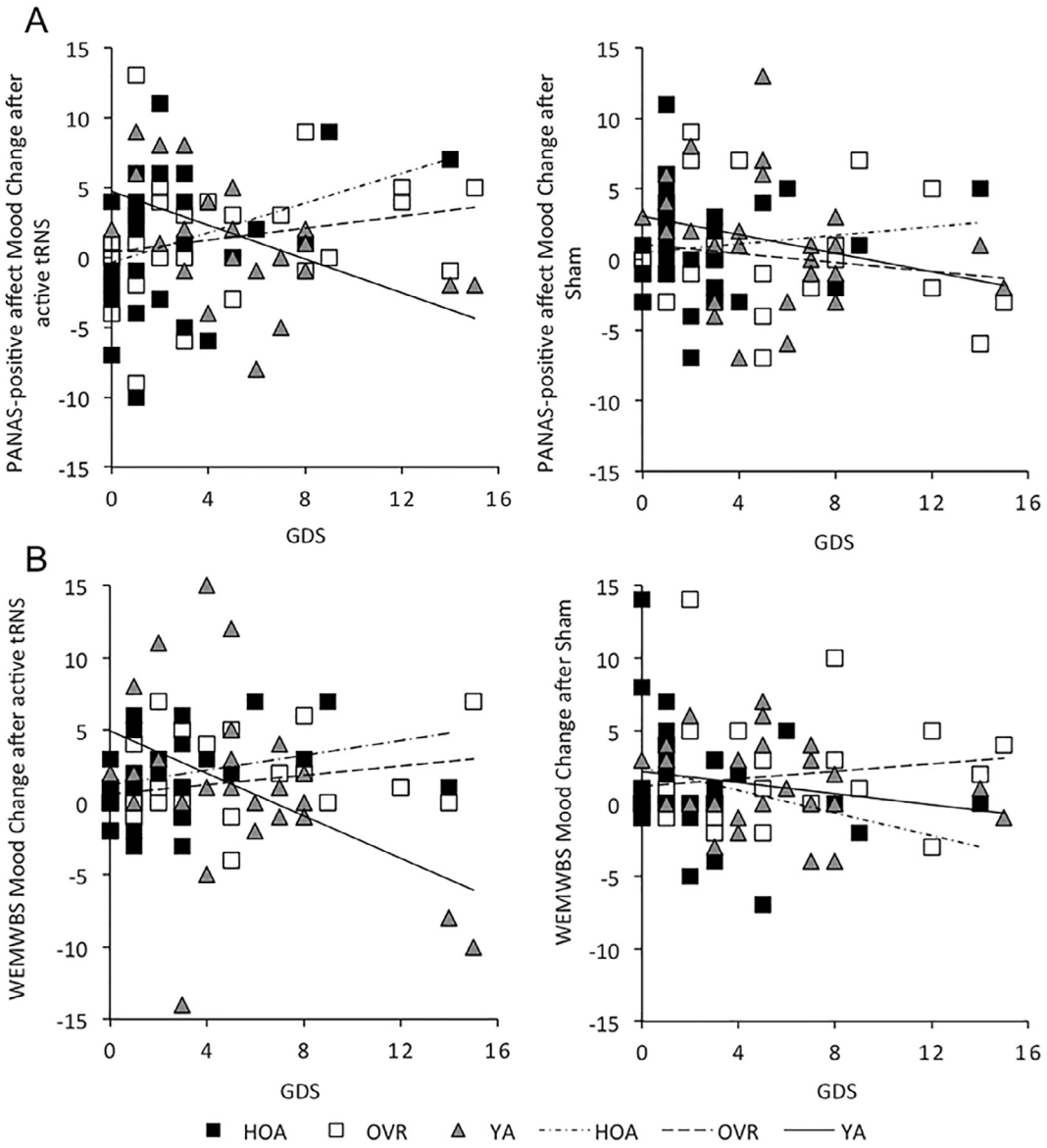

Fig. 1. A: PANAS-positive Mood Change after active-tRNS (left) and after Sham (right) in relation to GDS scores across all participant groups (YA/HOA/OVR). B: WEMWBS Mood Change after active-tRNS (left) and after Sham (right) in relation to GDS scores across all participant groups. For Mood Change a positive score indicated positive change in mood and a negative score indicated a negative change in mood. More positive GDS scores indicate more negative general mood and more negative GDS scores indicate more positive general mood.

Including baseline state mood: the inclusion of well-being score pre-stimulation as an additional predictor confirmed that baseline state mood did not significantly contribute to either model. During active-tRNS, the model significantly explained 17.0% of the variance in Mood Change ($F_{(6,79)} = 2.687$, $p = .020$, $R^2 = .170$, $R^2_{Adjusted} = .103$), whereas during sham, the model did not significantly explain variance in Mood Change ($F_{(6,79)} = 1.183$, $p = .324$, $R^2 = .082$, $R^2_{Adjusted} = .013$).

4. Discussion

This study examined the efficacy of tRNS to improve mood and whether this differs depending on individual differences in euthymic younger and older adults with and without CVRF. Results from two measures (PANAS-positive affect & WEMWBS) indicated that active-tRNS did not improve positive affect or well-being across all participants or within each participant group (YA/HOA/OVR), suggesting that tRNS was not sufficient in facilitating greater positive mood than a positive memory mood induction alone. Notably however, the patterns of response to active-tRNS appeared to differ depending on individual differences in age and trait mood. A small but significant proportion of the variance in positive affect after active-tRNS was explained by interaction terms for trait mood in the YA and HOA group. This trend was also observed for well-being, where the interaction term of trait mood and YA group reached significance. These results suggest that age and trait mood may be important variables affecting the efficacy of tES and are in line with a growing body of research emphasising the role of individual differences on the effect of stimulation.

Among older adults, individuals with lower trait mood reported the most positive change in mood after active-tRNS stimulation. This association was significant when mood was measured in terms of positive affect but did not reach significance for well-being. The relationship between trait mood and mood change after active-tRNS is positive and in keeping with some of the tDCS

results in YA with MDD (Boggio et al., 2008; Brunoni et al., 2014). This relationship, whereby HOA at most risk may show the greatest benefit, also follows a similar pattern to previous studies of tDCS applied to improve cognitive performance, where a relationship between baseline performance and response to stimulation has been observed (Berryhill and Jones, 2012; Learmonth et al., 2015). One explanation for these results is that those with the lowest mood have the greatest capacity for positive change. However, as the scores on all measures were not at ceiling for any group, all participants could have reported positive change in mood. Although the overall positive trait mood ratings were higher in the HOA group compared to YA, GDS scores alone did not significantly contribute to explaining the variance in tRNS response, suggesting that additional factors including age are influencing the effects of tRNS on mood. Coupled with the non-significant effect of tRNS on mood observed at a group level, the influence of age and trait mood on response to tRNS emphasises the importance of examining how individual differences may impact the efficacy of tES as a treatment for depression.

Whilst HOA with poorer trait mood showed the most positive change after tRNS, YA displayed the opposite pattern. In the current euthymic YA sample, applying tRNS bilaterally to DLPFC seemed to reduce mood state in those with lowest trait mood for both mood measures, positive affect and well-being. Yet, YA reporting more positive trait mood showed greater positive change. This pattern of results differs to previous studies that have shown reduced depressive symptoms in young adults with MDD when applying 1–2 mA of tDCS to the left DLPFC for approximately 20 min (Boggio et al., 2008; Ferrucci et al., 2009; Pérez et al., 2016).

It is possible that the relationship between tRNS and mood change in this euthymic adult sample is due to the use of bilateral DLPFC tRNS, which contrasts previous studies of young adults and those described here. For YA bilateral DLPFC tRNS could intensify the trait mood of the individual, therefore stimulation could be positive or negative depending on current mood (Feeser et al., 2014; Möbius et al., 2017). Due to reduced task-specific hemispheric asymmetry observed in older adults (Cabeza, 2002), bilateral stimulation was selected in an attempt to optimise the protocol for older adults. The relationship between trait mood and positive effects of tRNS observed in HOA in the current study support this theory. However it is important to note that it may be detrimental to young adults who do not typically rely on bilateral activation (Herrington et al., 2005). Bilateral tRNS to the DLPFC may have a different mechanism and effects compared to anodal tDCS over the left DLPFC (the most commonly used stimulation protocol). Only one previous case study in a 35-year-old woman with depression has demonstrated improvements in mood using bilateral DLPFC tRNS, although the cathode electrode was placed over F8 rather than F4 (Chan et al., 2012). The optimum stimulation protocol may therefore differ between younger and older adults.

As well as bilateral stimulation potentially having differing effects on younger and older adult populations, the effects of tRNS in this euthymic sample may be due to differences in the severity of depressive symptoms. However the regression model suggests that it is the interaction between depressive symptoms and age that is important. It is also worth noting that all groups described here reported normal mood levels and the effects of tRNS may differ in MDD or late-life depression. High-frequency tRNS may be most effective for improving mood in severe low mood where criteria for MDD are met. Research by Nitsche et al. (2012) suggest the effect of tDCS may be limited to emotion processing and not self-reported mood in healthy participants. Nevertheless, facilitatory effects have been noted elsewhere in the literature when using tDCS in healthy populations. TDCS has been shown to facilitate cognitive reappraisal both positively and negatively depending on the regulatory goal (Feeser et al., 2014). Although not a study of mood per se, Boggio and colleagues (Boggio et al., 2009) also demonstrated that healthy young adults reported less "unpleasantness" when viewing aversive stimuli, suggesting that lower mood is not necessary for tES to have an elevatory effect. It is worth noting that studies in MDD have reported mixed results, with some studies not demonstrating improvements in mood after tDCS (Nitsche et al., 2012; Palm et al., 2012), so other factors apart from depressive symptoms may influence response to stimulation (Loo et al., 2012).

One major issue raised by these results is the suggestion that individual differences including age and the level of depressive symptoms as well as interactions between such factors may influence response to tES for the elevation of mood. This is an important consideration for future studies using tES to modulate mood, as it highlights the importance of individual differences which may need careful consideration to optimise stimulation outcomes (Fertonani et al., 2016). Inter-individual differences in neurophysiology, anatomy, and psychology have been reported to result in substantial within- and between-group variances in response to tDCS (for reviews see Horvath et al., 2014; Krause and Cohen Kadosh, 2014). Though speculative, results suggest that individual differences may explain response to tES even in the absence of differences at the group level; when inter-individual variability can result in a different or even opposing response to tES, regressing to the mean of the sample may collapse any effect of tES that is occurring at an individual level. Another issue raised by the discrepancy in mood change across YA and HOA is the need to explore the anatomical specificity of these effects by comparing mood change across different electrode montages including stimulation of unilateral or bilateral DLPFC, and a control site. This was not explored in the current study as the focus was on individual differences and the efficacy of tRNS.

Another purpose of this study was to examine the effects of cardiovascular risk on response to tRNS in ageing. There were no significant differences between response to tRNS in the HOA compared to the OVR group, although the magnitude of the effect were lower in OVR. Although preliminary, the comparable relationship between age, trait mood, and response to tRNS suggest that tRNS may be as efficacious in OVR as in HOA. It is worth noting however that the OVR group described here does not include severe cardiovascular disease such as stroke, transient ischaemic attacks, or chronic obstructive pulmonary disease. Only one individual had diabetes (an additional participant was borderline), and 13 had diagnosed hypertension, with most individuals controlling their CVRF through diet and medication. Thus it remains to be established if the pattern reported here in individuals with relatively mild CVRF is comparable with more severe or uncontrolled cardiovascular disease. TRNS efficacy may reduce with severity of cardiovascular disease due to severity of damage in brain and disruption of neural networks (Alexopoulos, 2005). A limitation of this study was the lack of information about cardiovascular damage in the brain among older adults. Although one commonly observes strong associations between CVRF and cardiovascular damage in brain, individual differences do occur (Charlton et al., 2014). Future studies should aim to quantify cardiovascular damage in brain to fully explore the effect of cardiovascular disease on tES. This is particularly important if treatment controlled cardiovascular disease reduces the commonly associated cardiovascular damage.

It is important to acknowledge a number of study limitations that may also help understand the results observed in the current study. In the tRNS protocol, individuals received stimulation in a single session, which has been argued to be insufficient to affect mood in euthymic participants (for review see Remue et al., 2016). Mood was measured using self-report measures, which may be relatively insensitive to small changes in mood; using a

more objective measure (for example galvanic skin response, heart rate, etc) may be more sensitive to detecting changes. It is also feasible that multiple sessions may result in additive benefits that would be observable across each population at a group level. Although it is to be noted that our knowledge of how multiple sessions of stimulation contribute to interactions between cortical excitability and behaviour remains unclear (Batsikadze et al., 2013). Further, work in other domains shows that a single session of tRNS is sufficient to modulate behavioural outcomes at least temporarily (e.g. Romanska et al., 2015). In this study we were cautious of the deleterious effects of overstimulation, especially in an under-investigated group of older adults where the impact of age-related brain changes is unknown (Batsikadze et al., 2013; Nitsche and Paulus, 2011). Since this single-session protocol did not consistently improve mood across our participant groups, future studies may target repeated tRNS using this protocol or explore the efficacy of other levels of stimulation. As mood was measured immediately after stimulation sessions, any longer term effects of stimulation could not be observed. A longer follow-up would be required to examine the duration of effects. Studies of the effect of an intervention may also suffer from placebo effects, particularly when coupled with a positive mood induction (recall of positive memories in this instance). However the use of a double-blind design, tRNS with its low cutaneous effects, and both stimulation and sham sessions for participants should reduce any likely placebo effect.

The current study examined the efficacy of tRNS of the DLPFC to elevate mood in euthymic older and YAs. Whilst tRNS did not significantly improve mood across participants, response to tRNS seemed to depend on individual differences in age and trait mood. In HOA, more negative trait mood was associated with a greater positive mood change after tRNS. OVR showed a similar but reduced pattern of mood change to HOA, suggesting that mild CVRF may not overly disrupt tES effects. In YA, more positive trait mood was associated with greater positive mood change after tRNS, results may suggest an enhancement of current mood (whether positive or negative) after stimulation in YA. Age, trait mood and their interaction may be important factors when examining the efficacy of tES. Future studies should consider how individual differences interact with tES and affect response to stimulation.

Acknowledgements

The authors wish to thank all who participated in this study. The study was funded by the Dunhill Medical Trust, United Kingdom (R361/0514).

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

References

Alexopoulos G. Depression in the elderly. Lancet 2005;365(9475):1961–70.
Ambrus GG, Paulus W, Antal A. Cutaneous perception thresholds of electrical stimulation methods: comparison of tDCS and tRNS. Clin Neurophysiol 2010;121(11):1908–14. https://doi.org/10.1016/j.clinph.2010.04.020.
Bae JN, MacFall JR, Krishnan KRR, Payne ME, Steffens DC, Taylor WD. Dorsolateral prefrontal cortex and anterior cingulate cortex white matter alterations in late-life depression. Biol Psychiatry 2006;60(12):1356–63. https://doi.org/10.1016/j.biopsych.2006.03.052.
Batsikadze G, Moliadze V, Paulus W, Kuo M-F, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 2013;591:1987–2000. https://doi.org/10.1113/jphysiol.2012.249730.
Barch DM, D'Angelo G, Pieper C, Wilkins CH, Welsh-Bohmer K, Taylor W, et al. Cognitive improvement following treatment in late-life depression: relationship to vascular risk and age of onset. Am J Geriatr Psychiatry 2012;20(8):682–90. http://doi.org/10.1097/JGP.0b013e318246b6cb.
Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. Br J Psychiatry 1999;174(4):307 LP-311. Retrieved from <http://bjp.rcpsych.org/content/174/4/307.abstract>.
Berlim MT, Van den Eynde F, Daskalakis ZJ. A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. Psychol Med 2013;43(11):2245–54.
Berryhill ME, Jones KT. TDCS selectively improves working memory in older adults with more education. Neurosci Lett 2012;521(2):148–51. https://doi.org/10.1016/j.neulet.2012.05.074.
Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, et al. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol 2008;11(2):249–54. https://doi.org/10.1017/S1461145707007833.
Boggio PS, Zaghi S, Fregni F. Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia 2009;47(1):212–7. https://doi.org/10.1016/j.neuropsychologia.2008.07.022.
Brunoni AR, Boggio PS, De Raedt R, Bensenor IM, Lotufo PA, Namur V, et al. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. J Affect Disord 2014;162:43–9.
Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging 2002;17(1):85–100. https://doi.org/10.1037/0882-7974.17.1.85.
Chan HN, Alonzo A, Martin DM, Player M, Mitchell PB, Sachdev P, Loo CK. Treatment of major depressive disorder by transcranial random noise stimulation: case report of. Biol Psychiatry 2012;72(4):9–10. https://doi.org/10.1016/j.biopsych.2012.02.009.
Charlton RA, Lamar M, Zhang A, Yang S, Ajilore O, Kumar A. White-matter tract integrity in late-life depression: associations with severity and cognition. Psychol Med 2014;44(7):1427–37. https://doi.org/10.1017/S0033291713001980.
Feeser M, Prehn K, Kazzer P, Mungee A, Bajbouj M. Transcranial direct current stimulation enhances cognitive control during emotion regulation. Brain Stimul 2014;7(1):105–12. https://doi.org/10.1016/j.brs.2013.08.006.
Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Salvoro B, Giacopuzzi M, et al. Transcranial direct current stimulation in severe, drug-resistant major depression. J Affect Disord 2009;118:215–9.
Fertonani A, Miniussi C. Transcranial electrical stimulation: what we know and do not know about mechanisms. Neuroscientist, 2016. Feb 12. pii: 1073858416631966. http://doi.org/10.1177/1073858416631966.
Fertonani A, Pirulli C, Miniussi C. Random noise stimulation improves neuroplasticity in perceptual learning. J Neurosci 2011;31(43):15416–23. https://doi.org/10.1523/JNEUROSCI.2002-11.2011.
Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol Psychiatry 2008;63(4):369–76. https://doi.org/10.1016/j.biopsych.2007.05.033.
Grubbs FE. Procedures for detecting outlying observations in samples. Technometrics 1969;11(1):1–21. https://doi.org/10.1080/00401706.1969.10490657.
Herrington JD, Mohanty A, Koven NS, Fisher JE, Stewart JL, Banich MT, et al. Emotion-modulated performance and activity in left dorsolateral prefrontal cortex. Emotion 2005;5(2):200–7. https://doi.org/10.1037/1528-3542.5.2.200.
Horvath JC, Carter O, Forte JD. Transcranial direct current stimulation: five important issues we aren't discussing (but probably should be). Front Syst Neurosci 2014;8:2. https://doi.org/10.3389/fnsys.2014.00002.
Jorge RE, Moser DJ, Acion L, Robinson RG. Treatment of vascular depression using repetitive transcranial magnetic stimulation. Arch Gen Psychiatry 2008;65(3):268–76. https://doi.org/10.1001/archgenpsychiatry.2007.45.
Jorge RE, Robinson RG. Treatment of late-life depression: a role of non-invasive brain stimulation techniques. Int Rev Psychiatry 2011;23(5):437–44. https://doi.org/10.3109/09540261.2011.633501.
Kadosh RC. Using transcranial electrical stimulation to enhance cognitive functions in the typical and atypical brain. Transl Neurosci 2013;4(1):20–33. https://doi.org/10.2478/s13380-013-0104-7.
Kennedy KM, Raz N. Pattern of normal age-related regional differences in white matter microstructure is modified by vascular risk. Brain Res 2009;1297:41–56. https://doi.org/10.3816/CLM.2009.n.003.Novel.
Knopman DS, Penman AD, Catellier DJ, Coker LH, Shibata DK, Sharrett AR, et al. Vascular risk factors and longitudinal changes on brain MRI. The ARIC study. Neurology 2011;76(22):1879–85.
Koenigs M, Grafman J. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res 2009;201(2):239–43. https://doi.org/10.1016/j.bbr.2009.03.004.
Krause B, Cohen Kadosh R. Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. Front Syst Neurosci 2014;8:1–12. https://doi.org/10.3389/fnsys.2014.00025.
Learmonth G, Thut G, Benwell CSY, Harvey M. The implications of state-dependent tDCS effects in aging: behavioural response is determined by baseline performance. Neuropsychologia 2015;74:108–19. https://doi.org/10.1016/j.neuropsychologia.2015.01.037.

Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry 2012;200(1):52–9. https://doi.org/10.1192/bjp.bp.111.097634.

Manes F, Jorge R, Morcuende M, Yamada T, Paradiso S, Robinson RG. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. Int Psychogeriatrics 2001;13(2):225–31.

Meinzer M, Lindenberg R, Antonenko D, Flaisch T, Flöel A. Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. J Neurosci 2013;33(30):12470–8. https://doi.org/10.1523/JNEUROSCI.5743-12.2013.

Möbius M, Lacomblé L, Meyer T, Schutter DJLG, Gielkens T, Becker ES, et al. Repetitive transcranial magnetic stimulation modulates the impact of a negative mood induction. Soc Cogn Affect Neurosci 2017;12:526–33. https://doi.org/10.1093/scan/nsw180.

Molloy DW, Standish TI. A guide to the standardized Mini-Mental State Examination. Int Psychogeriatr 1997;9(Suppl 1):87–94; discussion 143–50. Retrieved from <http://europepmc.org/abstract/MED/9447431>.

Mosimann UP, Schmitt W, Greenberg BD, Kosel M, Müri RM, Berkhoff M, et al. Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. Psychiatry Res 2004;126(2):123–33. https://doi.org/10.1016/j.psychres.2003.10.006.

Nitsche MA, Koschack J, Pohlers H, Hullemann S, Paulus W, Happe S. Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans. Front Psychiatry 2012;3:1–10. https://doi.org/10.3389/fpsyt.2012.00058.

Nitsche MA, Paulus W. Transcranial direct current stimulation – update 2011. Restor Neurol Neurosci 2011;29(6):463–92. https://doi.org/10.3233/RNN-2011-0618.

O'Sullivan M, Jones DK, Summers PE, Morris RG, Williams SC, Markus HS. Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. Neurology 2001;57(4):632–8. https://doi.org/10.1212/WNL.57.4.632.

Palm U, Schiller C, Fintescu Z, Obermeier M, Keeser D, Reisinger E, et al. Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. Brain Stimul 2012;5(3):242–51. https://doi.org/10.1016/j.brs.2011.08.005.

Pascual-Leone A, Bartres-Faz D, Keenan JP. Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of "virtual lesions". Philos Trans R Soc Lond B Biol Sci 1999;354(1387):1229–38. https://doi.org/10.1098/rstb.1999.0476.

Pérez C, Leite J, Carvalho S, Fregni F. Transcranial electrical stimulation (tES) for the treatment of neuropsychiatric disorders across lifespan. Eur Psychol 2016. https://doi.org/10.1027/1016-9040/a000252.

Raz N, Rodrigue KM, Kennedy KM, Acker JD. Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. Neuropsychology 2007;21(2):149–57. https://doi.org/10.1037/0894-4105.21.2.149.

Remue J, Baeken C, De Raedt R. Does a single neurostimulation session really affect mood in healthy individuals? A systematic review. Neuropsychologia 2016. https://doi.org/10.1016/j.neuropsychologia.2016.03.012.

Romanska A, Rezlescu C, Susilo T, Duchaine B, Banissy MJ. High-frequency transcranial random noise stimulation enhances perception of facial identity. Cereb Cortex 2015;25(11):4334–40. https://doi.org/10.1093/cercor/bhv016.

Roose SP, Schatzberg AF. The efficacy of antidepressants in the treatment of late-life depression. J Clin Psychopharmacol 2005;25(4 Suppl 1):S1–7.

Ross LA, McCoy D, Coslett HB, Olson IR, Wolk DA. Improved proper name recall in aging after electrical stimulation of the anterior temporal lobes. Front Aging Neurosci 2011;3:1–8. https://doi.org/10.3389/fnagi.2011.00016.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120(12):2008–39. https://doi.org/10.1016/j.clinph.2009.08.016.

Shiozawa P, Da Silva ME, Dias DR, Chaves AC, De Oliveira Diniz BS, Cordeiro Q. Transcranial direct current stimulation for depression in a 92-year-old patient: a case study. Psychogeriatrics 2014;14(4):269–70. https://doi.org/10.1111/psyg.12100.

Shiozawa P, Fregni F, Benseñor IM, Lotufo PA, Berlim MT, Daskalakis JZ, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. Int J Neuropsychopharmacol 2014;17(9):1443–52. https://doi.org/10.1017/S1461145714000418.

Slotema CW, Dirk Blom J, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry 2010;71(7):873.

Taylor W, Aizenstein H, Alexopoulos G. The vascular depression hypothesis: mechanisms linking vascular disease with depression. Mol Psychiatry 2013;1820:963–74. https://doi.org/10.1038/mp.2013.20.

Tennant R, Hiller L, Fishwick R, Platt S, Joseph S, Weich S, et al. The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. Health Qual Life Outcomes 2007;5(1):63. https://doi.org/10.1186/1477-7525-5-63.

Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci 2008;28(52):14147–55. https://doi.org/10.1523/JNEUROSCI.4248-08.2008.

Verdelho A, Madureira S, Ferro JM, Basile A-M, Chabriat H, Erkinjuntti T, et al. Differential impact of cerebral white matter changes, diabetes, hypertension and stroke on cognitive performance among non-disabled elderly. The LADIS study. J Neurol, Neurosurg Psychiatry 2007;78(12):1325–330. Retrieved from <http://jnnp.bmj.com/cgi/content/long/78/12/1325>.

Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54(6):1063–70.

Wechsler D. Wechsler test of adult reading. San Antonio, USA: The Psychological Corporation; 2001.

Weintraub D, Saboe K, Stern MB. Effect of age on geriatric depression scale performance in Parkinson's disease. Mov Disord 2007;22(9):1331–5. https://doi.org/10.1002/mds.21369.

Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22(3):312–8. Retrieved from <http://stroke.ahajournals.org/content/22/3/312.abstract>.

Yesavage JA. Geriatric depression scale. Psychopharmacol Bull 1988;24(4):709–11. Retrieved from <http://europepmc.org/abstract/MED/3249773>.

Zimerman M, Hummel FC. Non-invasive brain stimulation: enhancing motor and cognitive functions in healthy old subjects. Front Aging Neurosci 2010;2:1–12. https://doi.org/10.3389/fnagi.2010.00149.