Highlights

- Effects of multi-session (m-)tDCS on verbal associative learning were investigated
- Active m-tDCS enhanced immediate learning in older adults
- Active m-tDCS enhanced long-term maintenance in both age-groups.
- Effects were most pronounced in individuals with lower baseline learning ability
- Effects were not exclusively due to enhanced memory consolidation

Multisession transcranial direct current stimulation facilitates verbal learning and memory consolidation in young and older adults

Garon Perceval[a,b], Andrew K. Martin[a,c], David A. Copland[a,d], Matti Laine[e], Marcus Meinzer[a,f*]

[a] The University of Queensland, Centre for Clinical Research, Brisbane, Australia

[b] Department of Psychology, School of Education, Soochow University, Suzhou, China

[c] University of Kent, Department of Psychology, Canterbury, UK

[d] The University of Queensland, School of Health and Rehabilitation Sciences, Brisbane, Australia

[e] Åbo Akademi University, Department of Psychology, Turku, Finland

[f] University Medicine Greifswald, Department of Neurology, Greifswald, Germany

*Corresponding author: University Medicine Greifswald, Greifswald, Germany, Tel. +49 170 7976170, e- mail: marcus.meinzer@med.uni-greifswald.de

Abstract

This study investigated effects of multisession transcranial direct-current stimulation on learning and maintenance of novel memory content and scrutinised effects of baseline cognitive status and the role of multi-session tDCS on overnight memory consolidation. In a prospective, randomized, double-blind, parallel-group, sham-tDCS controlled design, 101 healthy young and older adults completed a five-day verbal associative learning paradigm while receiving multisession tDCS to the task-relevant left prefrontal cortex. In older adults, active multisession tDCS enhanced recall performance after each daily training session. Effects were maintained the next morning and during follow-up assessments (one week; three months). In young adults, multisession tDCS significantly increased long-term recall. Unlike previous findings in the motor domain, beneficial effects of multisession tDCS on cognitive learning and memory were not exclusively due to enhanced memory consolidation. Positive stimulation effects were primarily found in participants with lower baseline learning ability, suggesting that multisession tDCS may counteract memory impairment in health and disease.

Keywords: multi-session transcranial direct current stimulation, aging, memory, learning, language, longitudinal design

1. Introduction

Problems in establishing and maintaining new memories are common in healthy aging and age-related disease (Kester, Benjamin, Castel, & Craik, 2002; Zacks, Hasher, & Li, 2000), reducing the quality of life and increasing the economic and social burden on aging societies on a global scale (Grady, 2012; D. C. Park & Reuter-Lorenz, 2009). Given that the proportion of elderly people in the population worldwide is expected to triple over the next 30-40 years(WHO, 2011), it is imperative to explore the effectiveness of novel interventions aimed at improving memory function in older adults. Transcranial direct current stimulation (tDCS) is one promising technique towards addressing this goal (Hsu, Juan, & Tseng, 2016; Perceval, Floel, & Meinzer, 2016; Summers, Kang, & Cauraugh, 2016). TDCS involves a weak electrical current administered to target brain regions via scalp-attached electrodes. Neural and behavioral effects during or immediately after a single tDCS session are mediated by short-lived modulation of the neural resting membrane potential, resulting in either enhanced or reduced neural excitability (Stagg & Nitsche, 2011). In aging, a growing number of proof-of-concept studies have demonstrated that single session tDCS can temporarily improve behavioral and brain function or even restore performance levels to those of young controls (for reviews see (Hsu et al., 2016; Perceval et al., 2016; Summers et al., 2016)).

However, to achieve longer-lasting behavioral and neural effects, tDCS needs to be administered over several days or weeks (i.e., multisession tDCS) and combined with behavioral training. Such protocols promote adaptive neuroplasticity via mechanisms similar to long-term potentiation (Cirillo et al., 2017). In young individuals, multisession tDCS has resulted in long-lasting (i.e., weeks to months) improvement of motor or cognitive learning (Cohen Kadosh, Soskic, Iuculano, Kanai, & Walsh, 2010; Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Hilgenstock, Weiss, Huonker, & Witte, 2016; Meinzer, Jahnigen, et al., 2014; Reis et al., 2009). Moreover, enhanced behavioral treatment effects have been demonstrated in different patient populations (Allman et al., 2016; Manenti et al., 2016; Meinzer, Darkow, Lindenberg, & Floel, 2016). In aging, multisession tDCS

studies that employed working memory training (Jones, Stephens, Alam, Bikson, & Berryhill, 2015; Stephens & Berryhill, 2016) or other cognitive training paradigms (Antonenko et al., 2017; S. H. Park, Seo, Kim, & Ko, 2014) have also demonstrated an improvement in specifically trained cognitive functions and provided preliminary evidence for enhanced transfer effects to untrained cognitive functions; but see Nilsson et al. (2017).

We expanded on these promising findings by training 101 healthy young and older adults on a verbal associative learning paradigm in a prospective, double-blind, sham-tDCS controlled study to address the following issues: (1) Because little is known about the time course of learning facilitation by multi-session tDCS, this was investigated across multiple time points (i.e., daily during the training period; 24 hrs, one week and three months later). (2) Multisession tDCS has been suggested to specifically affect memory consolidation (Reis et al., 2015). However, this has only been demonstrated in young individuals and by using procedural motor learning task. Here we probed whether the same mechanism explains potential cognitive multisession tDCS effects in young and older adults by investigating learning ability before and after each daily learning session. (3) Because several previous cross-sectional tDCS studies have shown that baseline cognitive ability can affect stimulation effectiveness (Berryhill & Jones, 2012; Learmonth, Thut, Benwell, & Harvey, 2015; Meinzer, Lindenberg, Antonenko, Flaisch, & Flöel, 2013) we included this factor in our analyses. We hypothesized that individuals with lower baseline ability would benefit most from the stimulation. (4) Since some previous studies have suggested that multisession tDCS may enhance transfer to untrained tasks (Antonenko et al., 2017; Cappelletti et al., 2013; S. H. Park et al., 2014), we hypothesized that multisession tDCS would enhance transfer to tasks that share common cognitive and neural components with the trained task (e.g., verbal learning or working memory).

2. MATERIALS AND METHODS

2.1. Study overview: The study employed a prospective, between-subjects, double-blind, placebo ("sham-tDCS") controlled design and was conducted at the Centre for Clinical Research at the

University of Queensland. We employed an explicit learning paradigm where 41 younger adults, and 60 healthy older adults were trained to learn associations between pictures of "space alien" characters (Gupta et al. 2004), their respective (non-word) names and two semantic attributes. The training was administered across five consecutive days. Participants received either active (anodal-tDCS) or placebo (sham-tDCS) stimulation of the left inferior frontal gyrus. IFG-tDCS was chosen, because this montage has been shown to induce neural modulation in a larger fronto-temporal network (Meinzer et al., 2012), overlapping with brain regions relevant for verbal associative learning (Laine & Salmelin, 2010; Rodriguez-Fornells, Cunillera, Mestres-Misse, & de Diego-Balaguer, 2009).

Prior to the learning phase, all participants were assessed for baseline cognitive status and completed a short version of the learning paradigm. Performance on the latter, along with age and sex, was used to randomly assign participants to the stimulation groups (see below). Learned associations were probed immediately prior to (except for day_1) and after each training day. This allowed us to investigate both immediate and delayed effects of active tDCS. Maintenance of learning success was assessed 24 hours, one week and three months after the end of the training. Short- and long-term transfer effects to untrained cognitive functions were assessed using a comprehensive and repeatable test battery. As baseline cognitive status predicted tDCS response in previous studies, we also investigated whether baseline learning ability would mediate tDCS effects. Blinding, adverse events and potential effects of tDCS on mood were systematically assessed. **Figure 1** illustrates the design of the study.

2.2. Participants: Participants were right-handed, healthy native English speakers from the Brisbane metropolitan area (Young group: 25 women, 16 men, mean±SD years: 21.44±3.61; Older group: 50 women, 10 men, mean±SD years: 67.05±6.00). None had previously participated in a tDCS study. Participants were excluded from the study according to standard tDCS safety criteria (e.g., if they had a history of seizures, metallic objects in the head or cardiac pacemakers, current depression or

other psychiatric condition (Bikson et al., 2016)). None of the younger participants reported to be on chronic medication, except for contraceptives (females). Several older participants reported to be on chronic prescription medicine; however, medication status was comparable in the stimulation groups (sham/anodal group: antihypertensives N=9/13, lipid lowering medication N=6/7, antidiuretics N=2/3, antidiabetics n=2/1, thyroid hormone replacement N=3/6, COPD puffers: N=1/1). None of the participants reported use of recreational drugs. All participants scored within normal (age-corrected) ranges during baseline cognitive testing (**Table 1**). Within each age-group, participants were pairwise stratified by age, sex and baseline learning ability on a short version of the learning paradigm and randomly assigned to the stimulation groups. This procedure resulted in two stimulation groups for each age group that were comparable regarding demographic characteristics, baseline cognitive status and learning ability (**Table 1)**. Written informed consent was obtained from each participant and the study was approved by the Human Research Ethics Committee of The University of Queensland. Participants received AUD$250 upon study completion.

2.3. Cognitive Screening: To ensure normal cognitive function, all participants completed a comprehensive neuropsychological test battery comprising tests used in the Australian Imaging, Biomarker and Lifestyle Study of Ageing (Ellis et al., 2009) that are known to have good reliability and validity. Tests covered a wide range of cognitive domains including language (vocabulary, naming, and fluency), executive functions, visual-spatial processing, working memory and learning (For details please see **Table 1**).

2.4. Experimental learning paradigm: We used an explicit verbal learning paradigm and participants were trained to learn associations between “space aliens” (Gupta et al., 2004), a non-word “name” and two semantic attributes. The training was administered across five consecutive weekdays (Mon-Fri between 8 am - 4 pm, based on individual preferences but at the same time of day for individual participants). Participants were instructed to memorize the names and attributes of each alien and were informed that they would be tested using three memory tasks immediately after the training

(assessing ***immediate after-effects*** of tDCS) and prior to the start of the training session on the next day (assessing ***long-term after-effects***; from day_2 on, including the day after the training ended). Our primary outcome measure was a ***free recall task*** that required written naming of each alien character. Secondary outcome measures were two recognition tasks that required a forced-choice decision between two non-word names (***name recognition***) or two sets of semantic attributes (***attribute recognition task***). To assess ***long-term maintenance*** of potential tDCS effects, the recall and recognition tasks were administered during two (one-week; three months) follow-up assessments.

2.4.1. Acquisition phase: 36 color images of "space aliens" were used (see **Figure 1B** for an example, (Gupta et al., 2004)). The aliens varied along three dimensions: head shape (human, N=12; vertically elongated, N=12; horizontally elongated, N=12), number of arms (two, N=18; four, N=18), and type of non-human appendage (tail, N=18; head appendage, N=18, (Gupta et al., 2004)). Each space alien character was presented together with a non-word "name" (e.g., Prute) and two semantic attributes (e.g., wise and heroic). 54 five-letter legal non-words were selected from the ARC Non-Word Database (Rastle, Harrington, & Coltheart, 2002). 36 of these non-words served as the name for each alien. 18 non-words were used as distractors in the forced-choice word recognition task (see below). 108 English adjectives served as non-visual, semantic attributes (word length: 5-6 letters). From this list, 54 pairs of adjectives were created so that both words matched for semantic congruency (e.g., 'wise - heroic', rather than 'wise - stupid'). 36 of these attribute pairs served as the attributes for each object. 18 pairs were used as distractors in the attribute recognition task (see below). Semantic attributes were included because semantic information has been suggested to facilitate learning (Angwin, Phua, & Copland, 2014).

The daily acquisition phase comprised 8 blocks with 9 trials in each block (in total 72 trials, with each of the 36 alien, name and attribute combinations presented twice daily in a pseudo-randomised order). Each trial began with a fixation cross presented in the centre of the screen for 1500 ms,

followed by the alien with its name and attributes for 8000 ms. Trials were separated by an interval of 500 ms. Participants were instructed to learn the names and attributes of each alien and were informed that they would subsequently be tested on their memory of these. During each block, the aliens and their names and attributes were presented automatically on a computer screen with white background. After each block, participants were prompted to take a short break and to press "space" to resume.

2.4.2. Recall and recognition tasks: All participants completed three memory tasks immediately after each training day, prior to the start of the next acquisition phase (from day2 on) and during the three follow-up assessments (24 hrs, 1 week, 3 months). During the ***free recall task***, all aliens were presented in random order on a white background and participants were instructed to use the computer keyboard to type the name into a space provided on the display below the image. Participants were instructed to type the whole name and to adhere to correct spelling. If they could not recall the whole name, participants were told that they could type part of the name or to take a guess at typing the whole name. If they were unable to produce a response, participants were instructed to press "enter" to continue to the next trial. The number of phonetically similar responses (e.g., "prute" rather than "proot") was very low (old adults: N=160 across all time points; 2.67/person, which is about 2% of approx. 8000 correct responses; young adults: N=51, 1.24/person, approx. 0.46% of approx. 11.000 correct responses). Therefore, only full word responses with correct spelling were scored as correct.

Afterwards, participants completed two forced-choice ***name*** and ***attribute recognition tasks***. Each recognition task comprised 36 trials and the aliens were presented on a white background with a selection of either two names or two attribute pairs at the bottom of the screen. Participants had to select the correct name or attribute pair for each alien using the left or right mouse buttons. During both recognition tasks, the distractors comprised 18 names or attributes assigned to other aliens

and 18 novel names and attributes (i.e., not assigned to other aliens). There was no time limit for any of the tasks.

2.5. Baseline learning ability: A short version of the explicit learning paradigm (12 different alien, word, attribute combinations) assessed baseline learning ability prior to the training. This short version of the paradigm comprised three acquisition trials, each followed immediately by free recall and name and attribute recognition trials. Learning success (# correctly recalled names) on this short version was used together with age and sex to stratify participants to the intervention groups. Although the stimulation groups did not differ in baseline learning ability (Younger: Sham, M=13.7, SD=5.58, Anodal, M=12.76, SD=7.47, p=0.65; Older: Sham, M=3.97, SD=3.83, Anodal, M=4.37, SD=4.44, p=0.71), older adults showed poorer baseline learning ability than younger adults ($p<0.001$). Baseline learning ability was also considered in the statistical analysis (see below).

2.6. Transfer effects: To assess potential transfer effects to untrained cognitive functions, the Cogstate computerized test battery (https://cogstate.com/) was administered immediately prior to and after the training period, as well as during the two long-term follow-up assessments. The test battery assessed a range of cognitive functions: processing speed, executive function, working memory, and verbal, visuospatial, and associative learning. It was chosen because it is repeatable, easy to administer, user-friendly, has good test-retest reliability(Cole et al., 2013), validity (Mielke et al., 2015), and is sensitive to assess change in cognitive functions that decline with age and in age-related cognitive disease (D. Darby, Maruff, Collie, & McStephen, 2002; D. G. Darby et al., 2012; Lim, Ellis, et al., 2013; Lim, Jaeger, et al., 2013).

2.7. Transcranial direct current stimulation: tDCS was administered using a battery-driven direct current stimulator (DC-Stimulator Plus, NeuroConn, Ilmenau, Germany). A pair of conductive rubber electrodes inserted into saline-soaked sponge pockets were used and attached to the scalp using rubber bands. The anode (5x7 cm^2) was placed over the left inferior frontal gyrus (left IFG), an area crucial for language learning (Rodriguez-Fornells et al., 2009). Moreover, because the left IFG is also

involved in a number of other cognitive processes like working memory (Nixon, Lazarova, Hodinott-Hill, Gough, & Passingham, 2004) and semantic retrieval (Meinzer et al., 2009; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997), we hypothesized that this montage would maximize both verbal learning and potential transfer effects. The location of the left IFG was determined using the EEG 10-20 system as described previously (Meinzer et al., 2012; Meinzer et al., 2013). The cathode (10x10 cm^2) was placed over the contralateral supraorbital region. The large size of the reference electrode renders the stimulation ineffective at this site without compromising the effect underneath the anode (Nitsche et al., 2007). The current was ramped up immediately prior to the acquisition phase over 10 seconds to 1 mA during both stimulation conditions. Afterwards, it remained constant for 20 min (anodal tDCS) or 40 seconds (sham-tDCS) before ramping down (over 10 sec). This protocol allows effective blinding of participants in the sham-tDCS group by inducing a similar physical sensation as in active stimulation without modulating neural activity (Gandiga, Hummel, & Cohen, 2006; Gbadeyan, Steinhauser, McMahon, & Meinzer, 2016). TDCS was administered during the acquisition phase (vs. retrieval phase) to maximize stimulation effects (Simonsmeier, Grabner, Hein, Krenz, & Schneider, 2017). Investigator blinding was achieved by the "study mode" of the DC stimulator where a predefined code triggered active or sham-tDCS. Codes were assigned by a researcher not involved in conducting the experiments.

2.8 Adverse effects and blinding: Adverse effects were assessed using a self-report questionnaire developed by Brunoni et al.(Brunoni et al., 2011). Participants rated the presence and intensity of a range of possible adverse events (1=absent, 2=mild, 3=moderate, 4=severe, see **Tables 2 and 3**). Participant blinding was assessed at the completion of training. Participants were asked the following: "What type of stimulation do you believe you received? (a) real stimulation, (b) placebo, or fake stimulation, or (c) unsure?"

2.9. Statistical analysis: Immediate and delayed effects of anodal-tDCS on recall and recognition performance over the five days of training (# correct items) and at follow-up (change scores, e.g.,

Change$_{24}$ =Day$_{5on}$-24-hrs) were analyzed using linear mixed effects models (Baayen, Davidson, & Bates, 2008; Verbeke & Molenberghs, 2000) with the lme4 package (Version 1.1.12, (Bates, Mächler, Bolker, & Walker, 2015)) in the R environment (Version 1.0.44; R Core Team 2014). Subject was modelled as a random effect using random-intercept models. The five time-points for the learning phase (TIME) for immediate effects of tDCS (i.e., after the end of each training session) were modelled as fixed effects. The analysis of delayed effects (i.e., the next morning) across the training phase comprised Days$_{2\text{-}5}$ and the short-term follow-up (24 hours). Long-term follow-up effects were modelled separately based on change scores (e.g., Change$_{24}$ =Day$_{5on}$-24-hrs) during the follow-up time points (24 hrs, 1 week, 3 months). Transfer effects were analyzed with linear mixed effects models for each Cogstate subtest by comparing pre-post training scores and scores across the three follow-up time-points.

For immediate and long-term after-effects (i.e., after training vs. the next morning), follow-up, and transfer data, the factors TIME, STIMULATION (anodal- vs. sham-tDCS), and AGEGROUP (young vs. older) served as fixed effects. Baseline learning ability (BASELINE) was included as a continuous covariate. The interactions TIME × STIMULATION assessed whether the slopes of the learning, follow-up, and transfer task curves differed between the stimulation and age-groups. The TIME × STIMULATION × BASELINE interactions assessed whether baseline learning ability influenced these effects. The TIME × STIMULATION × BASELINE × AGEGROUP interactions assessed for the impact of both baseline learning and age-group on these effects. To assess between-group differences in overnight memory decline across time, the same model was also used with change scores calculated between immediate and long-term after-effects (e.g., Change$_{1}$=Day$_{1imm}$–Day$_{2long}$). *P*-values were obtained using the Satterthwaite approximation to degrees of freedom via the lmerTest Package (Version 2.0-33, (Kuznetsova, Brockhoff, & Christensen, 2015)). Unstandardized regression coefficients (*B*), standard errors (SE), *F* values and significance levels are reported for all analyses. Please note, because of the skewed sex distribution in our sample (75 women, 26 men), we also

conducted an exploratory analysis that included sex as an additional co-variate in the statistical models. None of the significant effects were found to interact significantly with sex.

For display purposes, we also performed a hierarchical cluster analysis (Bailey, 1994) of the continuous baseline learning data with a 2-cluster solution using Ward's method (Ward, 1963) to generate a two-level categorical variable (Younger group: high learners, n=19; Anodal=9; low learners, n=22; Anodal=12; Older group: high learners, n=30; Anodal=14; low learners, n=30; Anodal=16). Figures relating to baseline learning illustrate data for these two subgroups. Detailed information about demographic and neuropsychological profiles of the groups resulting from the 2-cluster solution is provided in **Supplementary Tables 1+2.**

A 2x2 ANOVA (STIMULATION x AGEGROUP) assessed differences between the stimulation and age groups on the neuropsychological test battery. Linear mixed models assessed differences in adverse effects between stimulation and age groups over the five training days separately for each symptom. STIMULATION, TIME ($Day_{1\text{-}5}$), and AGEGROUP were included in models as fixed effects. Blinding success was evaluated using Chi^2-tests.

3. RESULTS

3.1. Baseline Cognitive Status, Adverse Effects, and Blinding

All participants performed within normal age ranges on the neuropsychological test battery. As expected, older adults performed worse than younger adults on a number of tests (see **Table 1**). Within each age-group, the two stimulation groups showed comparable neuropsychological profiles (Note: a significant difference on the Trail Making Test A in the younger group did not survive correcting for multiple comparisons). TDCS was well tolerated by participants of both age groups and only mild adverse effects were reported. Across both age-groups, no differences in the degree of reported adverse events in the two stimulation groups were found (all p's > 0.09, see **Tables 2 and 3**), except for tingling and scalp pain sensations: participants in the anodal group reported a greater

degree of tingling over time than sham (p=0.01), while participants in the sham group reported a greater degree of (mild) scalp pain (p=0.03). Age effects were also observed: the younger group reported a greater degree of headache, scalp pain, tingling, sleepiness and trouble concentrating than the older adults (p<0.001-p=0.049). A greater decrease in the degree of itching sensations over time was observed in the sham group, compared to anodal (p=0.02). Older adults in the anodal group reported a greater degree of tingling than sham (p=0.03). Participant blinding was successful. In the older group, only 23.3% of participants correctly guessed which type of stimulation they received (Incorrect: 38.3%, Unsure: 38.3%). In the young group, 39% guessed correctly (Incorrect: 46.3%, Unsure: 14.6%). There were no differences between stimulation groups concerning blinding results (Older: $\chi 2 = 0.902$, $p = 0.637$. Younger: $\chi 2 = 0.75$, $p = 0.686$).

3.2. Learning Data

3.2.1. Overall Sample (Young and Older Adults Combined)

First, we assessed immediate or delayed stimulation effects on learning rates over the five days of training, and whether this was specific to age-group membership or baseline learning ability.

3.2.2. Immediate after-effects of tDCS during the learning period ($Days_{1-5}$, see **Figures 2 and 3**)

Participants successfully learned the novel active vocabulary (TIME, $B = 8.00$, SE = 1.01, $F(1, 396) = 62.29$, $p<0.001$). A significant TIME × STIMULATION × AGEGROUP × BASELINE interaction was observed for the free-recall task ($B = -0.30$, SE = 1.14, $F(1, 396) = 4.70$, $p=0.03$), suggesting a specific effect of stimulation dependent on age-group membership and baseline learning ability. Subsequently, we performed two 3-way ANOVAs for each age group independently. A significant TIME × STIMULATION × BASELINE interaction was identified in the older adults ($B=-0.26$, SE=0.09, $F(1, 236)=7.67$, $p<0.01$), but not in the younger adults ($B = 0.04$, SE = 0.10, $F(1, 160) = 0.15$, $p=0.70$). To follow up on this interaction in older adults, we analysed the TIME × BASELINE interaction for each stimulation group independently. This interaction was stronger for the sham group (TIME ×

BASELINE, *B* = 0.64, SE = 0.07, *F*(1, 118)= 82.1, p<0.001) than for the group that had received anodal tDCS (TIME × BASELINE, *B* = 0.38, SE = 0.06, *F*(1, 118)= 38.83, p<0.001), suggesting that anodal tDCS weakened the impact of baseline ability on recall immediately after the end of the training. This means more pronounced benefits of anodal tDCS on learning ability were found specifically in participants with lower baseline learning scores. This effect is illustrated in **Figure 3.**

3.2.3. Long-term after-effects of tDCS during the learning period (day_2-24 hour follow-up, see **Figure 2 and 3**)

Recall performance as assessed prior to each training day improved across the training period (TIME, *B* = 7.59, SE = 0.98, *F*(1, 391.08)= 60.14, p<0.001). A significant TIME × STIMULATION *×* AGEGROUP *×* BASELINE interaction was observed (*B* = -0.32, SE = 0.13, *F*(1, 391.17) = 5.58, p=0.02) for long-term after-effects of tDCS on free-recall. Three-way ANOVAs were computed for each age group and a significant TIME × STIMULATION *×* BASELINE interaction was identified in the older adults (*B* = -0.31, SE = 0.09, *F*(1, 231.11) = 10.89, p<0.01), but not in the younger adults (*B* = 0.01, SE = 0.10, *F*(1, 160) = 0.02, p=0.89). To follow-up this interaction in the older adults, we analysed the TIME *×* BASELINE interaction for each stimulation group. The influence of this interaction was stronger for the sham group (TIME × BASELINE, *B* = 0.76, SE = 0.07, *F*(1, 114)= 109.04, p<0.001), than for anodal (TIME × BASELINE, *B* = 0.45, SE = 0.06, *F*(1, 117)= 61.33, p<0.001), suggesting that anodal tDCS weakened the impact of baseline ability on immediate learning. Therefore, stimulation also selectively improved learning in older adults with lower baseline ability (see **Figure 3)**.

For the older adults, there was no difference between groups in overnight decline scores across time (TIME × STIMULATION, *B*=0.02, SE=0.26, *F*(1,231.51)=0.01, p=0.93), indicating that the stimulation effects were not selectively induced by effects on overnight consolidation. Baseline learning ability did not further influence this null effect (TIME × STIMULATION × BASELINE, B=0.01, SE=0.05, F(1,230.96)=0.09, p=0.77).

In summary, we show a facilitatory effect of anodal-tDCS on immediate learning for the free recall task that is specific to older adults with lower baseline learning ability. These effects were maintained during the testing session on the next day. Performance on the easier forced choice name and attributed recognition tasks improved over time (all p's < 0.001), which demonstrates participant motivation and task compliance. No further significant effects were found for these tasks (see **Supplementary Table 1**).

3.3. Long-term maintenance – Free recall task (Day_5-3 month follow-up, see **Figure 4**)

During the learning phase, we observed age-related differences in stimulation response on the free-recall task. Therefore, to assess long-term maintenance effects, we analysed recall accuracy decline during the follow-up phase (24hrs, 1 week, 3 months) independently for young and older adults.

As expected, performance declined in both age groups during the three follow-up assessments (see **Figure 4A**). In the older group, decline scores were comparable between the two stimulation groups (TIME × STIMULATION, B = 0.57, SE = 1.51, F(1, 113.7) = 0.14, p=0.71), and baseline learning had no effect (TIME × STIMULATION × BASELINE, B = -0.28, SE = 0.27, F(1, 113.1) = 1.12, p=0.29). This suggests that stimulation-induced gains that were observed in older individuals with lower baseline performance during the learning phase, were maintained during the follow-up.

In the young group, the rate of decline was greater for the sham group than for the anodal tDCS group (TIME × STIMULATION, B = -7.78, SE = 3.41, F(1, 115) = 5.22, p=0.02). We also observed a significant TIME × STIMULATION × BASELINE interaction (B = 0.46, SE = 0.23, F(1, 115) = 43.92, p=0.049). Therefore, we inspected the effect of TIME × BASELINE in both stimulation conditions. Neither sham nor anodal stimulation resulted in a significant TIME × BASELINE interaction. For Sham, the TIME × BASELINE interaction was negative (B = -0.31, SE = 0.19, F(1, 56) = 2.49, p=0.12); for anodal stimulation the TIME × BASELINE interaction was positive (B = 0.15, SE = 0.13, F(1, 59) = 1.35, p=0.25). Therefore, stimulation differences were demonstrated at the level of the TIME ×

STIMULATION × BASELINE interaction, with anodal stimulation resulting in a greater effect of baseline learning on decline over time. Overall, this suggests that even in the absence of immediate stimulation effects on learning ability, learning gains were better maintained during the follow-up assessments (i.e., 1 week, 3 months) in younger individuals with lower baseline learning scores who had received anodal-tDCS (**Figure 4C**).

3.4. Transfer effects

No baseline differences were found between active and sham stimulation groups for any of the Cogstate subtests (STIMULATION, all p = 0.06 – 1.00). Age-group membership had no further effect (STIMULATION × AGEGROUP, all p = 0.09 – 0.94). There were some significant effects of stimulation at different time points and for different tests (see **Tables 4 and 5**). However, none of them survived correcting for multiple comparisons. Therefore, no substantial transfer effects were observed and the stimulation groups were comparable in their performance across time on all Cogstate subtests (TIME × STIMULATION, pre vs. post: p = 0.02 – 0.93; follow-up: p = 0.01 – 0.95). Including age-group or baseline learning ability in the analysis did not further alter this outcome (TIME × STIMULATION × AGEGROUP, pre vs. post: p = 0.04 – 0.92; follow-up: p = 0.01– 0.95; TIME × STIMULATION × BASELINE, pre vs. post: p = 0.04 – 0.97; follow-up: p = 0.01 – 0.92).

4. DISCUSSION

This study demonstrated that multisession tDCS can improve verbal associative learning and its long-term maintenance in healthy older adults. Importantly, beneficial tDCS effects were not exclusively explained by overnight consolidation. In younger individuals, no immediate effects of tDCS were found, but active tDCS reduced memory decline during the long-term follow-up sessions. In both age-groups, beneficial effects of multisession tDCS were most pronounced in individuals with lower baseline learning capacity. This shows that both short- and long-term tDCS effects are dependent on baseline cognitive status. Our result thus emphasizes that tDCS is particularly suited to improve

learning and memory formation in those individuals who require such a “boost”. However, it is worth noting that multisession tDCS did not “restore” learning and memory in lower-functioning (older) adults to the level of young individuals or high-functioning older participants. Blinding was successful in both age-groups and only mild adverse effects were reported. Therefore, our study also adds to the growing literature demonstrating that positive effects of multisession tDCS on brain function can be achieved without side effects, making it an attractive tool for cognitive enhancement in advanced age (Kortteenniemi, Ali-Sisto, Wikgren, & Lehto, 2017). Unlike previous studies that reported near transfer effects to untrained materials (Antonenko et al., 2017; S. H. Park et al., 2014), such effects were absent in the present study. This highlights a task-specific effect of tDCS on brain activity elicited during learning and memory formation. Note that in a recent meta-analysis by Nilsson et al. (2017) that failed to find beneficial effects of tDCS during cognitive training, the outcome measures mixed transfer and training tasks, thus being uninformative of effects on trained tasks.

Overall, young and older participants in both stimulation conditions showed evidence of learning associations between the alien characters and their respective names and attributes across the five training days, but there was also substantial variability in performance within each group. Importantly, active tDCS selectively improved learning ability only in individuals with lower baseline learning performance. Although potential tDCS effects in the high-performing subgroup may have been masked by near ceiling effects on the two easier recognition tasks, learning curves were comparable (in older adults almost identical) for active and sham-tDCS even for the more difficult name recall task where there was a substantial room for improvement even in high performers. These results suggest that baseline cognitive status is an important factor in determining stimulation effectiveness (Silvanto, Muggleton, & Walsh, 2008). This is in line with previous cross-sectional research showing that tDCS effects in elderly participants are modified by factors such as baseline task performance and lateralization of brain activity (Berryhill & Jones, 2012; Learmonth et al., 2015; Meinzer et al., 2013). While it has been suggested that brains already functioning at a near optimal

406 ("homeostatic") level may not respond to tDCS in the same way as those with suboptimal activity
407 (Brem, Fried, Horvath, Robertson, & Pascual-Leone, 2014; Krause, Márquez-Ruiz, & Kadosh, 2013),
408 neural mechanisms underlying such modifying factors are not well understood, even in healthy
409 young individuals (Hsu et al., 2016; Martin, Huang, Hunold, & Meinzer, 2017; Tseng et al., 2012). This
410 needs to be scrutinized in future imaging studies by investigating baseline brain network structure
411 and training-induced changes related to the facilitatory effects of multisession tDCS.

412 Our results also demonstrate that the beneficial short-term effects of tDCS in low-performing older
413 adults were mainly due to acute stimulation effects, which were largely maintained during the
414 assessments on the morning of the following training day. To the best of our knowledge, only two
415 previous studies aimed to address the temporal locus of multisession tDCS effects (Reis et al., 2015;
416 Reis et al., 2009) with both studies testing younger individuals [Please note, only one of these
417 studies (Reis et al. 2015) allowed investigation of true "offline" or long-term after-effects by
418 including a training block without concurrent tDCS]. Both studies used a motor sequence learning
419 task with concurrent tDCS and did not find immediate performance improvement. However,
420 profound effects on memory consolidation were reported several hours after the end of the training
421 (Reis et al., 2015) or after a period of sleep (Reis et al., 2015; Reis et al., 2009). A number of tentative
422 explanations may explain these differences. First, memory consolidation for procedural (Reis et al.,
423 2015; Reis et al., 2009) vs. explicit episodic memory content (i.e., the present study) is supported by
424 different neural systems (Plihal & Born, 1997). Procedural memory has been linked to basal ganglia
425 and cortico-cerebellar networks, while episodic memory requires the hippocampus and neocortical
426 structures relevant for specific tasks (Harand et al., 2012; Squire, 2004). There may also be
427 differences in the optimal timing depending on the experimental context or task and other motor
428 learning studies have demonstrated beneficial effects of tDCS when administered shortly after the
429 end of the training (e.g., Tecchio et al. 2010; Rumpf et al. 2017). TDCS may thus act differently on
430 different memory systems, irrespective of age, but there is also evidence for reduced (overnight)
431 memory consolidation in advanced age (Gudberg, Wulff, & Johansen-Berg, 2015; Harand et al.,

2012). Moreover, only one recent study investigated the impact of multisession tDCS on learning ability using an implicit object location learning paradigm (Antonenko et al., 2017). This study also failed to find immediate stimulation effects on performance, which only became evident immediately after a three-day training period, being maintained during a one month follow-up assessment. It is worth noting that across the entire sample, tDCS did not result in immediate performance improvement in the present study, and positive effects were limited to the subgroup of low performers. As none of the previous multisession tDCS studies considered baseline cognitive status or learning ability in their analysis, potential subgroup effects may have been missed. Therefore, future studies are urgently needed to disentangle the contribution of chronological age, target memory systems, and task characteristics on the temporal dynamics of multisession tDCS response. Nonetheless, the results of our study did not provide support for the notion that tDCS exclusively acts on memory consolidation mechanisms. This is also in line with a previous study from our group that demonstrated immediate beneficial effects on verbal associative learning ability in young participants (Meinzer, Jahnigen, et al., 2014). In contrast, no immediate effects were found in the present younger sample, which is likely explained by the design of this study. Specifically, in an attempt to keep the learning paradigm comparable for young and older adults and to account for reduced learning ability in aging, the present study used relatively few picture-name pairs (N=36) compared to our previous study (N=120; Meinzer et al. (2014)). Therefore, task demands were substantially different. Nonetheless, beneficial long-term stimulation effects in the young group were found (a) in those individuals that found the task “more challenging” (i.e., low performers) and (b) during delayed memory retrieval (i.e., the follow-up assessments). Both findings are in line with a task difficulty account that impacted multisession tDCS effects in the present study.

We also observed that tDCS-induced learning gains were largely maintained for up to three months after the end of the training. This is in line with previous multisession tDCS studies in young adults demonstrating long-term beneficial stimulation effects that outlasted the end of the training for at least one week and up to one year (Cohen Kadosh et al., 2010; Dockery et al., 2009; Meinzer,

458 Jahnigen, et al., 2014; Reis et al., 2009). In older adults, only a handful of studies combined cognitive
459 training (Jones et al., 2015; S. H. Park et al., 2014) or learning paradigms (Antonenko et al., 2017)
460 with multisession tDCS. These studies reported beneficial effects that were maintained for up to one
461 month. Moreover, several multisession tDCS studies in both young (Richmond, Wolk, Chein, & Olson,
462 2014) and older (Antonenko et al., 2017; Jones et al., 2015; S. H. Park et al., 2014; Stephens &
463 Berryhill, 2016) individuals also reported transfer effects to untrained cognitive tasks. In the present
464 study, we did not find evidence for any transfer effects, which suggests a rather specific impact of
465 tDCS on brain networks activated by the associative learning task. However, it needs to be
466 acknowledged that transfer effects in older adults were mainly found for closely related tasks (near
467 transfer tasks), which was not tested in the present study. In addition, in comparison to learning
468 paradigms, successful transfer may be more likely with general cognitive training approaches (S. H.
469 Park et al., 2014).

470 **5. Conclusions**

471 We have demonstrated that multisession tDCS enhances both immediate and delayed learning in
472 older adults with lower baseline learning ability and that these effects were maintained for up to
473 three months. While no immediate effects were found in young adults, the rate of forgetting over
474 time was reduced by the stimulation in this group. Future studies employing fMRI are needed to
475 investigate the underlying neural mechanisms responsible for such enhancement, and the baseline
476 neural characteristics predicting stimulation response in low performers. In sum, we demonstrated
477 that multisession tDCS is a viable method for improving verbal learning and memory performance in
478 healthy young and older individuals. The fact that these effects were mainly found in lower
479 performing individuals opens the possibility that it may also be suited for clinical populations such as
480 patients with mild cognitive impairment (Meinzer, Lindenberg, et al., 2014).

481

Acknowledgements

This work was supported by grants from the Australian Research Council (ARC FT120100608 to M.M. and D.A.C); the National Health and Medical Research Council (#1085272 to M.M. and D.A.C); the University of Queensland Vice Chancellor's Research and Teaching Fellowship (to D.C.); the Academy of Finland (project #260276 to M.L.); and the Åbo Akademi University Endowment (The BrainTrain project grant to M.L.).

References

Allman, C., Amadi, U., Winkler, A. M., Wilkins, L., Filippini, N., Kischka, U., . . . Johansen-Berg, H. (2016). Ipsilesional anodal tDCS enhances the functional benefits of rehabilitation in patients after stroke. *Sci Transl Med, 8*(330), 330re331. doi:10.1126/scitranslmed.aad5651

Angwin, A. J., Phua, B., & Copland, D. A. (2014). Using semantics to enhance new word learning: an ERP investigation. *Neuropsychologia, 59*, 169-178. doi:10.1016/j.neuropsychologia.2014.05.002

Antonenko, D., Kulzow, N., Sousa, A., Prehn, K., Grittner, U., & Floel, A. (2017). Neuronal and behavioral effects of multi-day brain stimulation and memory training. *Neurobiol Aging, 17*, 30313-30315. doi:10.1016/j.neurobiolaging.2017.09.017

Baayen, R. H., Davidson, D. J., & Bates, D. M. (2008). Mixed-effects modeling with crossed random effects for subjects and items. *J Mem Lang, 59*(4), 390-412. doi.org/10.1016/j.jml.2007.12.005

Bailey, K. D. (1994). *Typologies and Taxonomies: An Introduction to Classification Techniques*. Thousand Oaks (CA): SAGE Publications.

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *J Stat Softw, 67*(1), 48.. doi:10.18637/jss.v067.i01

Berryhill, M. E., & Jones, K. T. (2012). tDCS selectively improves working memory in older adults with more education. *Neurosci Lett, 521*(2), 148-151. doi:10.1016/j.neulet.2012.05.074

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., . . . Woods, A. J. (2016). Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. *Brain Stimul, 9*(5), 641-661.. doi:10.1016/j.brs.2016.06.004

Brem, A. K., Fried, P. J., Horvath, J. C., Robertson, E. M., & Pascual-Leone, A. (2014). Is neuroenhancement by noninvasive brain stimulation a net zero-sum proposition? *Neuroimage, 85 Pt 3*, 1058-1068. doi:10.1016/j.neuroimage.2013.07.038

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol, 14*(8), 1133-1145. doi:10.1017/s1461145710001690

Cappelletti, M., Gessaroli, E., Hithersay, R., Mitolo, M., Didino, D., Kanai, R., . . . Walsh, V. (2013). Transfer of cognitive training across magnitude dimensions achieved with concurrent brain stimulation of the parietal lobe. *J Neurosci, 33*(37), 14899-14907. doi:10.1523/jneurosci.1692-13.2013

Cirillo, G., Di Pino, G., Capone, F., Ranieri, F., Florio, L., Todisco, V., . . . Di Lazzaro, V. (2017). Neurobiological after-effects of non-invasive brain stimulation. *Brain Stimul, 10*(1), 1-18. doi:10.1016/j.brs.2016.11.009

Cohen Kadosh, R., Soskic, S., Iuculano, T., Kanai, R., & Walsh, V. (2010). Modulating neuronal activity produces specific and long-lasting changes in numerical competence. *Curr Biol, 20*(22), 2016-2020. doi:10.1016/j.cub.2010.10.007

Cole, W. R., Arrieux, J. P., Schwab, K., Ivins, B. J., Qashu, F. M., & Lewis, S. C. (2013). Test-retest reliability of four computerized neurocognitive assessment tools in an active duty military population. *Arch Clin Neuropsychol, 28*(7), 732-742. doi:10.1093/arclin/act040

Darby, D., Maruff, P., Collie, A., & McStephen, M. (2002). Mild cognitive impairment can be detected by multiple assessments in a single day. *Neurology, 59*(7), 1042-1046.

Darby, D. G., Pietrzak, R. H., Fredrickson, J., Woodward, M., Moore, L., Fredrickson, A., . . . Maruff, P. (2012). Intraindividual cognitive decline using a brief computerized cognitive screening test. *Alzheimers Dement, 8*(2), 95-104. doi:10.1016/j.jalz.2010.12.009

Dockery, C. A., Hueckel-Weng, R., Birbaumer, N., & Plewnia, C. (2009). Enhancement of planning ability by transcranial direct current stimulation. *J Neurosci, 29*(22), 7271-7277. doi:10.1523/jneurosci.0065-09.2009

Ellis, K. A., Bush, A. I., Darby, D., De Fazio, D., Foster, J., Hudson, P., . . . Ames, D. (2009). The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. *Int Psychogeriatr, 21*(4), 672-687. doi:10.1017/s1041610209009405

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol, 117*(4), 845-850. doi:10.1016/j.clinph.2005.12.003

Gbadeyan, O., Steinhauser, M., McMahon, K., & Meinzer, M. (2016). Safety, tolerability, blinding efficacy and behavioural effects of a novel MRI-compatible, High-Definition tDCS set-up. *Brain Stimul, 9*(4), 545-552. doi:10.1016/j.brs.2016.03.018

Grady, C. (2012). The cognitive neuroscience of ageing. *Nat Rev Neurosci, 13*(7), 491-505. doi:10.1038/nrn3256

Gudberg, C., Wulff, K., & Johansen-Berg, H. (2015). Sleep-dependent motor memory consolidation in older adults depends on task demands. *Neurobiol Aging, 36*(3), 1409-1416. doi:10.1016/j.neurobiolaging.2014.12.014

Gupta, P., Lipinski, J., Abbs, B., Lin, P. H., Aktunc, E., Ludden, D., . . . Newman, R. (2004). Space aliens and nonwords: stimuli for investigating the learning of novel word-meaning pairs. *Behav Res Methods Instrum Comput, 36*(4), 599-603.

Harand, C., Bertran, F., Doidy, F., Guenole, F., Desgranges, B., Eustache, F., & Rauchs, G. (2012). How aging affects sleep-dependent memory consolidation? *Front Neurol, 3*, 8. doi:10.3389/fneur.2012.00008

Hilgenstock, R., Weiss, T., Huonker, R., & Witte, O. W. (2016). Behavioural and neurofunctional impact of transcranial direct current stimulation on somatosensory learning. *Hum Brain Mapp, 37*(4), 1277-1295. doi:10.1002/hbm.23101

Hsu, T. Y., Juan, C. H., & Tseng, P. (2016). Individual Differences and State-Dependent Responses in Transcranial Direct Current Stimulation. *Front Hum Neurosci, 10*, 643. doi:10.3389/fnhum.2016.00643

Jones, K. T., Stephens, J. A., Alam, M., Bikson, M., & Berryhill, M. E. (2015). Longitudinal neurostimulation in older adults improves working memory. *PLoS One, 10*(4), e0121904. doi:10.1371/journal.pone.0121904

Kester, J. D., Benjamin, A. S., Castel, A. D., & Craik, F. I. M. (2002). Memory in elderly people. In A. D. Baddeley, Kopelman, M.D., Wilson, B.A. (Ed.), *The handbook of memory disorders* (2nd ed., pp. 543-567). Chichester (Great Britain): John Wiley & Son, Ltd.

Kortteenniemi, A., Ali-Sisto, T., Wikgren, J., & Lehto, S. (2017). Transcranial direct current stimulation: Adverse effects and the efficacy of a commonly utilised sham protocol. *Eur Psychiatry, 41*, S374. doi:10.1016/j.eurpsy.2017.02.392

Krause, B., Márquez-Ruiz, J., & Kadosh, R. C. (2013). The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? *Front Hum Neurosci, 7*, 602. doi:10.3389/fnhum.2013.00602

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2015). lmerTest: tests in linear mixed effects models. R package version 2.0-20. *URL: https://cran.rproject.org/web/packages/lmerTest. Accessed, 15*, 2016.

Laine, M., & Salmelin, R. (2010). Neurocognition of New Word Learning in the Native Tongue: Lessons From the Ancient Farming Equipment Paradigm. *Lang Learn, 60*, 25-44. doi:10.1111/j.1467-9922.2010.00599.x

Learmonth, G., Thut, G., Benwell, C. S., & Harvey, M. (2015). The implications of state-dependent tDCS effects in aging: Behavioural response is determined by baseline performance. *Neuropsychologia, 74*, 108-119. doi:10.1016/j.neuropsychologia.2015.01.037

Lim, Y. Y., Ellis, K. A., Harrington, K., Pietrzak, R. H., Gale, J., Ames, D., . . . Maruff, P. (2013). Cognitive decline in adults with amnestic mild cognitive impairment and high amyloid-beta: prodromal Alzheimer's disease? *J Alzheimers Dis, 33*(4), 1167-1176. doi:10.3233/jad-121771

Lim, Y. Y., Jaeger, J., Harrington, K., Ashwood, T., Ellis, K. A., Stoffler, A., . . . Maruff, P. (2013). Three-month stability of the CogState brief battery in healthy older adults, mild cognitive impairment, and Alzheimer's disease: results from the Australian Imaging, Biomarkers, and Lifestyle-rate of change substudy (AIBL-ROCS). *Arch Clin Neuropsychol, 28*(4), 320-330. doi:10.1093/arclin/act021

Manenti, R., Brambilla, M., Benussi, A., Rosini, S., Cobelli, C., Ferrari, C., . . . Cotelli, M. (2016). Mild cognitive impairment in Parkinson's disease is improved by transcranial direct current stimulation combined with physical therapy. *Mov Disord, 31*(5), 715-724. doi:10.1002/mds.26561

Martin, A. K., Huang, J., Hunold, A., & Meinzer, M. (2017). Sex mediates the effects of high-definition transcranial direct current stimulation on "mind-reading". *Neuroscience, 366*, 84-94. doi:10.1016/j.neuroscience.2017.10.005

Meinzer, M., Antonenko, D., Lindenberg, R., Hetzer, S., Ulm, L., Avirame, K., . . . Flöel, A. (2012). Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. *J Neurosci, 32*(5), 1859-1866. doi:10.1523/jneurosci.4812-11.2012

Meinzer, M., Darkow, R., Lindenberg, R., & Floel, A. (2016). Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia. *Brain, 139*(Pt 4), 1152-1163. doi:10.1093/brain/aww002

Meinzer, M., Flaisch, T., Wilser, L., Eulitz, C., Rockstroh, B., Conway, T., . . . Crosson, B. (2009). Neural signatures of semantic and phonemic fluency in young and old adults. *J Cogn Neurosci, 21*(10), 2007-2018. doi:10.1162/jocn.2009.21219

Meinzer, M., Jahnigen, S., Copland, D. A., Darkow, R., Grittner, U., Avirame, K., . . . Floel, A. (2014). Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary. *Cortex, 50*, 137-147. doi:10.1016/j.cortex.2013.07.013

Meinzer, M., Lindenberg, R., Antonenko, D., Flaisch, T., & Flöel, A. (2013). Anodal transcranial Direct Current Stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. *J Neurosci, 33*(30), 12470-12478. doi:10.1523/jneurosci.5743-12.2013

Meinzer, M., Lindenberg, R., Phan, M. T., Ulm, L., Volk, C., & Floel, A. (2014). Transcranial direct current stimulation in mild cognitive impairment: Behavioral effects and neural mechanisms. *Alzheimers Dement, 11*(9), 1032-1040. doi:10.1016/j.jalz.2014.07.159

Mielke, M. M., Machulda, M. M., Hagen, C. E., Edwards, K. K., Roberts, R. O., Pankratz, V. S., . . . Petersen, R. C. (2015). Performance of the CogState computerized battery in the Mayo Clinic Study on Aging. *Alzheimers Dement, 11*(11), 1367-1376. doi:10.1016/j.jalz.2015.01.008

Nilsson, J., Lebedev, A. V., Rydstrom, A., & Lovden, M. (2017). Direct-Current Stimulation Does Little to Improve the Outcome of Working Memory Training in Older Adults. *Psychol Sci, 28*(7), 907-920.. doi:10.1177/0956797617698139

Nitsche, M. A., Doemkes, S., Karakose, T., Antal, A., Liebetanz, D., Lang, N., . . . Paulus, W. (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J Neurophysiol, 97*(4), 3109-3117. doi:10.1152/jn.01312.2006

Nixon, P., Lazarova, J., Hodinott-Hill, I., Gough, P., & Passingham, R. (2004). The inferior frontal gyrus and phonological processing: an investigation using rTMS. *J Cogn Neurosci, 16*(2), 289-300. doi:10.1162/089892904322984571

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol, 60*, 173-196. doi:10.1146/annurev.psych.59.103006.093656

Park, S. H., Seo, J. H., Kim, Y. H., & Ko, M. H. (2014). Long-term effects of transcranial direct current stimulation combined with computer-assisted cognitive training in healthy older adults. *Neuroreport, 25*(2), 122-126. doi:10.1097/wnr.0000000000000080

Perceval, G., Floel, A., & Meinzer, M. (2016). Can transcranial direct current stimulation counteract age-associated functional impairment? *Neurosci Biobehav Rev, 65*, 157-172. doi:10.1016/j.neubiorev.2016.03.028

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *J Cogn Neurosci, 9*(4), 534-547. doi:10.1162/jocn.1997.9.4.534

Rastle, K., Harrington, J., & Coltheart, M. (2002). 358,534 nonwords: the ARC Nonword Database. *Q J Exp Psychol A, 55*(4), 1339-1362. doi:10.1080/02724980244000099

Reis, J., Fischer, J. T., Prichard, G., Weiller, C., Cohen, L. G., & Fritsch, B. (2015). Time- but not sleep-dependent consolidation of tDCS-enhanced visuomotor skills. *Cereb Cortex, 25*(1), 109-117. doi:10.1093/cercor/bht208

Reis, J., Schambra, H. M., Cohen, L. G., Buch, E. R., Fritsch, B., Zarahn, E., . . . Krakauer, J. W. (2009). Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proc Natl Acad Sci U S A, 106*(5), 1590-1595. doi:10.1073/pnas.0805413106

Richmond, L. L., Wolk, D., Chein, J., & Olson, I. R. (2014). Transcranial direct current stimulation enhances verbal working memory training performance over time and near transfer outcomes. *J Cogn Neurosci, 26*(11), 2443-2454. doi:10.1162/jocn_a_00657

Rodriguez-Fornells, A., Cunillera, T., Mestres-Misse, A., & de Diego-Balaguer, R. (2009). Neurophysiological mechanisms involved in language learning in adults. *Philos Trans R Soc Lond B Biol Sci, 364*(1536), 3711-3735. doi:10.1098/rstb.2009.0130

Rumpf, J.J., Wegscheider, M., Hinselmann, M., Fricke, C., King, B. R., Weise, D., Klann, J., … Classen., J. (2017). Enhancement of motor consolidation by post-training transcranial direct current stimulation in older people. *Neurobiol Aging,* 49:1-8 doi:10.1016/j.neurobiolaging.2016.09.003

Silvanto, J., Muggleton, N., & Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends Cogn Sci, 12*(12), 447-454. doi:10.1016/j.tics.2008.09.004

Simonsmeier, B. A., Grabner, R. H., Hein, J., Krenz, U., & Schneider, M. (2017). Electrical Brain Stimulation (tES) Improves Learning More Than Performance: A Meta-Analysis. *Neurosci Biobehav Rev, 17*, 30317-30312. doi:https://doi.org/10.1016/j.neubiorev.2017.11.001

Squire, L. R. (2004). Memory systems of the brain: a brief history and current perspective. *Neurobiol Learn Mem, 82*(3), 171-177. doi:10.1016/j.nlm.2004.06.005

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist, 17*(1), 37-53. doi:10.1177/1073858410386614

Stephens, J. A., & Berryhill, M. E. (2016). Older Adults Improve on Everyday Tasks after Working Memory Training and Neurostimulation. *Brain Stimul, 9*(4), 553-559. doi:10.1016/j.brs.2016.04.001

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A Compendium of neuropsychological tests: Administration, norms, and commentary*. New York (NY): Oxford University Press.

Summers, J. J., Kang, N., & Cauraugh, J. H. (2016). Does transcranial direct current stimulation enhance cognitive and motor functions in the ageing brain? A systematic review and meta- analysis. *Ageing Res Rev, 25*, 42-54. doi:10.1016/j.arr.2015.11.004

Tecchio, F., Zappasodi, F., Assenza, G., Tombini, M., Vollaro, S., Barbati, G., Rossini, P. M. (2010). Anodal transcranial direct current stimulation enhances procedural consolidation. *J Neurophysiol* 104(2):1134-40 doi: 10.1152/jn.00661.2009

Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., & Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. *Proc Natl Acad Sci U S A, 94*(26), 14792-14797.

Tseng, P., Hsu, T.-Y., Chang, C.-F., Tzeng, O. J. L., Hung, D. L., Muggleton, N. G., . . . Juan, C.-H. (2012). Unleashing potential: Transcranial Direct Current Stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. *J Neurosci, 32*(31), 10554-10561. doi:10.1523/jneurosci.0362-12.2012

Verbeke, G., & Molenberghs, G. (2000). *Linear mixed model for longitudinal data*. New York (NY): Springer.

690 Ward, J. H. (1963). Hierarchical grouping to optimize an objective function. *J Am Stat Assoc, 58*(301),
691 236-244. doi:10.1080/01621459.1963.10500845
692 WHO. (2011). *Global health and aging* (Vol. NIH Publication no. 11-7737).
693 Zacks, R. T., Hasher, L., & Li, K. Z. H. (2000). Human memory. In F. I. M. Craik & T. A. Salthouse (Eds.),
694 *The handbook of aging and cognition.* (2nd ed.). Mahwah, NJ: Lawrence Erlbaum Associates,
695 Inc.
696

Table 1. Demographic and neurocognitive profiles of young and older participants in the two stimulation groups (anodal-; sham- tDCS), means ± standard deviation are reported

	Younger			Older			Age-group Comparison
	Sham-tDCS	Anodal-tDCS	Signif.	Sham-tDCS	Anodal-tDCS	Signif.	Signif.
Age (yrs)	21.25 ± 3.97	21.62 ± 3.32	0.75	67.4 ± 6.08	66.7 ± 6.05	0.66	<.001*
Sex (men/women)	8/12	8/13		6/24	4/26		
Education (yrs)	14.25 ± 1.29	14.62 ± 1.12	0.33	14.07 ± 2.36	14.17 ± 1.90	0.86	0.38
MMSE[1]	29.95 ± 0.22	29.86 ± 0.36	0.33	29.47 ± 0.86	29.67 ± 0.76	0.30	0.01
D-KEFS[1]	(Scaled score)						
Semantic Fluency	44.05 ± 6.83	44.19 ± 8.98	0.96	44.3 ± 10.54	45.67 ± 8.73	0.59	0.06
	(12.6 ± 2.82)	(12.57 ± 3.31)	(0.98)	(13.47 ± 3.73)	(14.23 ± 3.22)	(0.40)	(0.64)
Phonemic Fluency	40.85 ± 8.69	42.76 ± 10.52	0.53	46.53 ± 15.03	48.43 ± 11.12	0.58	0.02
	(11.7 ± 2.89)	(12.05 ± 3.02)	(0.71)	(13.23 ± 4.33)	(13.80 ± 3.06)	(0.56)	(0.02)
Boston Naming Test[1#]	14.20 ± 0.89	14.43 ± 1.08	0.47	14.37 ± 1.03	14.40 ± 1.16	0.91	0.76

Trail Making Test A[2]	23.75 ± 6.53	19.13 ± 3.86	0.01	29.23 ± 7.75	29.53 ± 8.76	0.89	<.001*
Trail Making Test B	49.96 ± 16.92	47.99 ± 15.80	0.70	63.28 ± 27.62	65.87 ± 19.03	0.67	<.001*
HLVT[1]	(T-scores)						
Total Recall	30.70 ± 2.47	28.81 ± 4.27	0.09	26.90 ± 4.71	28.83 ± 4.71	0.12	0.04
	(57.17 ± 7.83)	(60.00 ± 7.02)	(0.36)	(47.07 ± 12.12)	(53.92 ± 12.83)	(0.17)	(0.60)
Delayed Recall	11.50 ± 0.76	10.62 ± 1.91	0.06	9.62 ± 2.40	10.10 ± 1.81	0.43	<0.01
	(57.17 ± 5.41)	(57.5 ± 5.28)	(0.88)	(45.86 ± 11.58)	(51.08 ± 8.32)	(0.19)	(0.47)
Retention (%)	94.89 ± 9.96	89.60 ± 14.66	0.19	89.27 ± 17.30	91.53 ± 10.66	0.54	0.52
	(51.6 ± 6.65)	(48.14 ± 9.74)	0.19	(50.13 ± 8.53)	(51.07 ± 6.62)	0.64	(0.44)
D-KEFS[2]	(Scaled Scores)						
Colour Naming	26.96 ± 4.83	26.06 ± 3.73	0.50	30.31 ± 6.24	30.49 ± 5.28	0.91	<.001*
	(10.35 ± 2.35)	(10.71 ± 1.79)	(0.56)	(10.07 ± 2.55)	(10.87 ± 2.26)	(0.75)	(0.35)
Word Reading	20.07 ± 3.20	20.33 ± 4.54	0.83	23.11 ± 5.18	22.48 ± 3.44	0.58	<0.01
	(11.15 ± 1.95)	(10.95 ± 2.71)	(0.79)	(10.93 ± 2.63)	(11.23 ± 1.72)	(0.60)	(0.94)

Inhibition	42.77 ± 7.88	43.17 ± 7.22	0.87	54.41 ± 11.92	54.37 ± 10.03	0.99	<.001*
	(11.95 ± 1.79)	(11.81 ± 1.66)	(0.80)	(12.70 ± 2.15)	(12.53 ± 1.68)	(0.74)	(0.05)
Inhibition/Switching	51.96 ± 10.66	51.91 ± 7.47	0.99	59.80 ± 13.95	58.92 ± 11.33	0.79	0.002*
	(11.20 ± 2.33)	(11.14 ± 1.65)	(0.93)	(12.53 ± 1.91)	(12.57 ± 1.77)	(0.94)	(<.001*)
RBANS							
Figure Copy[2]	18.40 ± 1.67	17.67 ± 1.80	0.19	19.17 ± 1.23	18.73 ± 1.44	0.22	<0.01
Figure Copy Delay[2]	16.70 ± 2.00	15.29 ± 3.18	0.10	15.07 ± 3.26	14.00 ± 2.49	0.16	0.01
Digit Span[1]	11.90 ± 2.27	12.33 ± 2.61	0.58	12.07 ± 2.35	12.37 ± 2.34	0.62	0.84
Symbol Coding	58.95 ± 8.18	61.05 ± 9.88	0.47	48.47 ± 9.06	49.83 ± 7.48	0.53	<.001*
Story Memory[1]	18.45 ± 2.54	19.19 ± 2.42	0.35	17.83 ± 3.60	17.50 ± 2.73	0.69	0.06
NART							
NART Error	18.65 ± 6.63	18.67 ± 4.43	0.99	11.30 ± 6.77	11.43 ± 6.22	0.94	<.001*
NART IQ	112.25 ± 5.50	112.24 ± 3.71	0.99	118.38 ± 5.61	118.07 ± 5.00	0.82	<.001*

HADS							
Depression	2.10 ± 1.65	2.71 ± 2.45	0.36	2.40 ± 1.77	2.70 ± 2.55	0.60	0.76
Anxiety	5.35 ± 3.22	6.71 ± 3.54	0.21	4.80 ± 3.21	4.97 ± 3.32	0.84	0.09

699 *Note*. MMSE, Mini Mental State Examination; D-KEFS, Delis-Kaplan Executive Function System; HVLT, Hopkins Verbal Learning Test; RBANS,
700 Repeatable Battery for the Assessment of Neuropsychological Status; NART, National Adult Reading Test; HADS, Hospital Anxiety and Depression
701 Scale (For a review of all tests, see Strauss et al. (2006)).[1]Number of correct responses. [2]Response latency (seconds). [#]15-item version.
702 *($p<0.05/23=p<0.002$).

703

704 **Table 2.** Adverse effects reported by younger participants in both stimulation groups (anodal-, sham-tDCS) as assessed after the end of each daily
705 stimulation session¸ means ± standard deviation are reported

Symptom	StimGroup	Day 1	Day 2	Day 3	Day 4	Day 5	Between-group comparison
Headache	Anodal	1.33 ± 0.58	1.33 ± 0.48	1.29 ± 0.56	1.24 ± 0.44	1.19 ± 0.51	p = 0.76
	Sham	1.25 ± 0.55	1.40 ± 0.68	1.20 ± 0.41	1.20 ± 0.41	1.20 ± 0.41	
Neck pain	Anodal	1.29 ± 0.56	1.19 ± 0.40	1.14 ± 0.36	1.19 ± 0.40	1.10 ± 0.30	p = 0.62
	Sham	1.25 ± 0.55	1.10 ± 0.31	1.05 ± 0.22	1.05 ± 0.22	1.05 ± 0.22	
Scalp pain	Anodal	1.10 ± 0.30	1.10 ± 0.30	1.14 ± 0.48	1.14 ± 0.36	1.10 ± 0.30	p = 0.12
	Sham	1.30 ± 0.57	1.20 ± 0.52	1.15 ± 0.37	1.10 ± 0.31	1.15 ± 0.37	
Tingling	Anodal	1.83 ± 0.10	1.93 ± 0.10	1.87 ± 0.11	1.73 ± 0.11	1.77 ± 0.11	p = 0.17
	Sham	1.70 ± 0.10	1.57 ± 0.11	1.57 ± 0.11	1.53 ± 0.11	1.50 ± 0.11	
Itching	Anodal	1.90 ± 0.77	2.05 ± 0.74	1.95 ± 0.67	2.00 ± 0.71	1.95 ± 0.67	p = 0.51
	Sham	2.05 ± 0.95	1.80 ± 0.70	1.75 ± 0.64	1.65 ± 0.59	1.55 ± 0.61	
Burning	Anodal	1.86 ± 0.91	1.95 ± 0.97	1.86 ± 0.96	1.71 ± 0.90	1.71 ± 0.85	p = 0.29
	Sham	1.60 ± 0.75	1.70 ± 0.80	1.70 ± 0.66	1.80 ± 0.83	1.50 ± 0.69	
Sleepiness	Anodal	2.19 ± 1.03	1.95 ± 1.02	2.05 ± 1.02	2.24 ± 1.00	1.62 ± 0.67	p = 0.84
	Sham	2.35 ± 0.81	2.10 ± 0.85	1.80 ± 0.77	2.05 ± 0.76	1.90 ± 0.91	

Concentration	Anodal	1.76 ± 0.70	1.38 ± 0.74	1.43 ± 0.60	1.43 ± 0.68	1.38 ± 0.74	p = 0.85
	Sham	1.75 ± 0.72	1.40 ± 0.60	1.50 ± 0.83	1.55 ± 0.83	1.50 ± 0.83	
Mood Change	Anodal	1.14 ± 0.36	1.10 ± 0.44	1.10 ± 0.30	1.10 ± 0.30	1.19 ± 0.51	p = 0.68
	Sham	1.15 ± 0.37	1.10 ± 0.31	1.00 ± 0.00	1.10 ± 0.31	1.05 ± 0.22	

Table 3. Adverse effects reported by older participants in both stimulation groups (anodal-, sham-tDCS) as assessed after the end of each daily stimulation session¸ means ± standard deviation are reported

Symptom	StimGroup	Day 1	Day 2	Day 3	Day 4	Day 5	Between-group comparison
Headache	Anodal	1.10 ± 0.31	1.07 ± 0.25	1.10 ± 0.31	1.03 ± 0.18	1.03 ± 0.18	p = 0.99
	Sham	1.10 ± 0.31	1.10 ± 0.40	1.07 ± 0.25	1.10 ± 0.31	1.03 ± 0.18	
Neck pain	Anodal	1.17 ± 0.46	1.13 ± 0.35	1.10 ± 0.31	1.07 ± 0.25	1.10 ± 0.31	p = 0.36
	Sham	1.07 ± 0.37	1.10 ± 0.40	1.07 ± 0.25	1.03 ± 0.18	1.03 ± 0.18	
Scalp pain	Anodal	1.03 ± 0.18	1.00 ± 0.00	1.03 ± 0.18	1.00 ± 0.00	1.00 ± 0.00	p = 0.28
	Sham	1.07 ± 0.25	1.10 ± 0.31	1.07 ± 0.25	1.00 ± 0.00	1.07 ± 0.25	
Tingling	Anodal	1.83 ± 0.59	1.93 ± 0.64	1.87 ± 0.63	1.73 ± 0.69	1.77 ± 0.68	p = 0.11
	Sham	1.70 ± 0.54	1.57 ± 0.50	1.57 ± 0.57	1.53 ± 0.51	1.50 ± 0.51	
Itching	Anodal	1.50 ± 0.73	1.40 ± 0.72	1.33 ± 0.55	1.33 ± 0.61	1.37 ± 0.62	p = 0.44
	Sham	1.33 ± 0.55	1.27 ± 0.52	1.23 ± 0.50	1.17 ± 0.38	1.20 ± 0.41	
Burning	Anodal	1.20 ± 0.11	1.23 ± 0.57	1.20 ± 0.48	1.30 ± 0.65	1.13 ± 0.35	p = 0.31
	Sham	1.47 ± 0.63	1.20 ± 0.41	1.30 ± 0.54	1.33 ± 0.48	1.30 ± 0.47	
Sleepiness	Anodal	1.40 ± 0.77	1.20 ± 0.48	1.20 ± 0.48	1.13 ± 0.51	1.13 ± 0.35	p = 0.22
	Sham	1.17 ± 0.53	1.30 ± 0.65	1.20 ± 0.48	1.27 ± 0.52	1.17 ± 0.46	

Concentration	Anodal	1.30 ± 0.54	1.13 ± 0.35	1.10 ± 0.31	1.17 ± 0.46	1.03 ± 0.18	p = 0.93
	Sham	1.10 ± 0.31	1.27 ± 0.64	1.17 ± 0.46	1.10 ± 0.31	1.03 ± 0.18	
Mood Change	Anodal	1.03 ± 0.18	1.00 ± 0.00	1.10 ± 0.40	1.00 ± 0.00	1.00 ± 0.00	p = 0.10
	Sham	1.10 ± 0.40	1.07 ± 0.37	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	

712 **Table 4.** Assessment of transfer effects in younger participants of both stimulation groups. Means ± standard deviation are reported
713

	Pre-test		*24 hours*		*1 week*		*3 months*	
	Sham-tDCS	Anodal-tDCS	Sham-tDCS	Anodal-tDCS	Sham-tDCS	Anodal-tDCS	Sham-tDCS	Anodal-tDCS
International Shopping list[1]	29.5 ± 2.61	28.24 ± 2.25	29.5 ± 3.52	28.90 ± 2.86	30.50 ± 3.03	29.24 ± 3.71	30.75 ± 3.78	30.14 ± 3.02
Groton Maze Learning[2]	40.75 ± 9.40	38.81 ± 9.22	35.45 ± 10.29	41.14 ± 9.75	35.05 ± 11.08	34.43 ± 7.83	32.20 ± 8.53	37.67 ± 11.23
Detection test[3]	2.50 ± 0.04	2.52 ± 0.05	2.55 ± 0.07	2.53 ± 0.04*^{ab}	2.51 ± 0.04	2.54 ± 0.07	2.51 ± 0.06	2.53 ± 0.06
Identification test[3]	2.65 ± 0.04	2.67 ± 0.06	2.69 ± 0.06	2.68 ± 0.05^{ac}	2.69 ± 0.06	2.70 ± 0.06	2.68 ± 0.06	2.69 ± 0.05
One Card Learning[4]	1.06 ± 0.08	1.06 ± 0.09	1.10 ± 0.12	1.09 ± 0.12	1.08 ± 0.11	1.06 ± 0.09	1.05 ± 0.13	1.08 ± 0.11
One Back[4]	1.40 ± 0.10	1.40 ± 0.15	1.36 ± 0.13	1.40 ± 0.11*^{b}	1.41 ± 0.12	1.44 ± 0.14	1.36 ± 0.15	1.38 ± 0.13$^{\#+fg}$
Two Back[4]	1.36 ± 0.13	1.30 ± 0.15	1.37 ± 0.16	1.31 ± 0.16	1.38 ± 0.18	1.36 ± 0.14	1.37 ± 0.20	1.38 ± 0.14
Set Shifting[2]	18.40 ± 12.27	20.67 ± 10.20	20.30 ± 12.91	19.24 ± 8.23	21.30 ± 9.77	18.10 ± 8.12	22.45 ± 12.93	18.05 ± 5.90^{+def}
Continuous Paired Associative Learning[2]	24.50 ± 18.71	29.57 ± 25.28	17.30 ± 27.03	25.33 ± 30.86	14.90 ± 25.58	19.33 ± 39.95	14.80 ± 25.48	18.90 ± 35.51

Social-Emotional Cognition[4]	1.15 ± 0.07	1.13 ± 0.07	1.16 ± 0.11	1.13 ± 0.08	1.16 ± 0.10	1.18 ± 0.10	1.14 ± 0.14	1.16 ± 0.09
International Shopping List (Delayed Recall)[1]	10.55 ± 1.82	10.48 ± 1.36	10.80 ± 1.47	10.33 ± 1.74	10.60 ± 1.50	10.48 ± 1.54	10.60 ± 1.50	10.62 ± 1.75
Groton Maze Learning (Delayed Recall)[2]	3.55 ± 2.74	5.14 ± 3.38	4.75 ± 2.63	6.14 ± 4.55	4.40 ± 3.07	4.52 ± 2.86	3.80 ± 2.40	4.95 ± 3.23

[1]Number of correct responses. [2]Number of errors. [3]Speed of performance (lower score = better performance). [4]Accuracy of performance (higher score = better performance).

Between group analysis: *p<0.05 (Pre-test – 24 hours, Time × StimGroup); #p<0.05 (24 hours – 3 months, StimGroup), +p<0.05 (24 hours – 3 months, Time × StimGroup).

Old/Young combined analysis: [a]p<0.05 (Pre-test – 24 hours, Time × StimGroup), [b]p<0.05 (Pre-test – 24 hours, Time × StimGroup × AgeGroup), [c]p<0.05 (Pre-test – 24 hours, Time × StimGroup × Baseline), [d]p<0.05 (Pre-test – 24 hours, Time × StimGroup), [e]p<0.05 (24 hours – 3 months, Time × StimGroup × AgeGroup), [f]p<0.05 (24 hours – 3 months, Time × StimGroup × Baseline), [g]p<0.01 (24 hours – 3 months, Time × StimGroup × AgeGroup)

723 **Table 5.** Assessment of transfer effects in older participants of both stimulation groups. Means ± standard deviation are reported

	Pre-test		*24 hours*		*1 week*		*3 months*	
	Sham-tDCS	Anodal-tDCS	Sham-tDCS	Anodal-tDCS	Sham-tDCS	Anodal-tDCS	Sham-tDCS	Anodal-tDCS
International Shopping list[1]	25.61 ± 3.53	26.46 ± 2.86	27.68 ± 3.81	27.96 ± 3.60	27.66 ± 4.11	28.21 ± 3.36	28.62 ± 3.91	28.53 ± 3.15
Groton Maze Learning[2]	56.46 ± 16.66	54.61 ± 13.99	48.11 ± 13.93	48.67 ± 16.92	45.24 ± 17.25	44.34 ± 13.37	47.96 ± 19.80	44.47 ± 12.85
Detection test[3]	2.57 ± 0.09	2.53 ± 0.09	2.58 ± 0.10	2.55 ± 0.09[ab]	2.57 ± 0.08	2.54 ± 0.08	2.58 ± 0.09	2.55 ± 0.09
Identification test[3]	2.74 ± 0.05	2.72 ± 0.06	2.76 ± 0.09	2.72 ± 0.05[ac]	2.75 ± 0.05	2.72 ± 0.05	2.75 ± 0.06	2.72 ± 0.06
One Card Learning[4]	1.02 ± 0.07	1.01 ± 0.10	1.02 ± 0.09	1.04 ± 0.09	1.03 ± 0.09	1.03 ± 0.08	1.04 ± 0.08	1.04 ± 0.08
One Back[4]	1.37 ± 0.14	1.38 ± 0.16	1.44 ± 0.10	1.43 ± 0.11[b]	1.45 ± 0.13	1.43 ± 0.10	1.40 ± 0.14	1.40 ± 0.12[fg]
Two Back[4]	1.26 ± 0.11	1.23 ± 0.09	1.27 ± 0.13	1.28 ± 0.12	1.35 ± 0.15	1.31 ± 0.13	1.30 ± 0.16	1.30 ± 0.12
Set Shifting[2]	16.61 ± 10.04	14.71 ± 4.41	14.36 ± 7.46	11.70 ± 3.48	13.03 ± 5.32	11.76 ± 2.46	15.89 ± 9.44	12.77 ± 4.96[def]
Continuous Paired Associative Learning[2]	81.21 ± 45.85	76.50 ± 41.94	75.36 ± 60.63	52.74 ± 42.46	59.00 ± 43.90	50.55 ± 49.65	54.00 ± 57.53	54.23 ± 42.12

Social-Emotional Cognition[4]	1.12 ± 0.15	1.11 ± 0.08	1.13 ± 0.16	1.16 ± 0.09	1.13 ± 0.18	1.17 ± 0.06	1.14 ± 0.17	1.16 ± 0.08
International Shopping List (Delayed Recall)[1]	8.86 ± 1.94	9.04 ± 1.64	9.61 ± 1.66	9.48 ± 2.10	8.97 ± 2.11	9.21 ± 1.92	9.62 ± 1.70	9.90 ± 1.79
Groton Maze Learning (Delayed Recall)[2]	9.36 ± 3.99	10.61 ± 3.65	8.58 ± 3.43	8.07 ± 3.00	8.62 ± 4.30	8.14 ± 3.59	8.23 ± 3.55	8.13 ± 3.43

[1]Number of correct responses. [2]Number of errors. [3]Speed of performance (lower score = better performance). [4]Accuracy of performance (higher score = better performance).

Old/Young combined analysis: [a]$p<0.05$ (Pre-test – 24 hours, Time × StimGroup), [b]$p<0.05$ (Pre-test – 24 hours, Time × StimGroup × AgeGroup), [c]$p<0.05$ (Pre-test – 24 hours, Time × StimGroup × Baseline), [d]$p<0.05$ (Pre-test – 24 hours, Time × StimGroup), [e]$p<0.05$ (24 hours – 3 months, Time × StimGroup × AgeGroup), [f]$p<0.05$ (24 hours – 3 months, Time × StimGroup × Baseline), [g]$p<0.01$ (24 hours – 3 months, Time × StimGroup × AgeGroup)

Figure Captions

Figure 1. Study Design: A. Overview of training and testing sessions from day 1 to 3 month follow-up. Day 1 begins with acquisition of name + object pairings and simultaneous stimulation (anodal- or sham-tDCS) and is followed by immediate recall and recognition tasks. Days 2-5 comprise delayed recall and recognition tasks. This is followed by acquisition and stimulation phases and immediate recall and recognition tasks. 24 hour to 3 month follow-ups comprise recall and recognition tasks and assessment of transfer to untrained functions using the Cogstate battery. **B.** Shows acquisition phase and recall and recognition tasks. During acquisition, each novel object picture is presented with the matching non-word and two semantic attributes. During recall the object picture is presented and participants are instructed to type the correct names. During the recognition tasks the object picture is presented with a choice of two nonwords/sets of attributes and participants are instructed to select the correct nonword/set of attribute.

Figure 2. Learning phase in both age groups: Displays accuracy scores (# correct) for the recall task assessed immediately after the end of each daily training session ("imm") and the morning of the next day ("del" refers to delayed after-effects of tDCS). Shown are day 1 to the 24 hour follow-up (FU) for the primary outcome measure (name recall) and the entire sample of young and older adults.

Figure 3. Learning phase older adults split by baseline learning ability: Displays accuracy scores (# correct) for the recall task assessed immediately after the end of each daily training session ("imm") and the morning of the next day ("del" refers to delayed after-effects of tDCS). Shown are day 1 to the 24 hour follow-up (FU) for the primary outcome measure (name recall) for older participants with high and low baseline learning ability. Data shows that tDCS-induced learning gains were more

pronounced in the low performing older group that had received anodal tDCS. More pronounced learning at the end of day 5 and the short-term follow up (24 hrs) amounted to 86.7% and 75.4% respectively (Effect size d'=.64/.74; i.e., medium effect sizes). Please note, figures are for illustrative purposes only. In the main results we report baseline performance as a continuous variable.

Figure 4. Displays decline scores for correctly recalled names (# correct) for the follow-up time-points relative to the end of the last training day. (A) Entire sample, (B) participants with high or (C) low learning ability during the baseline assessment. Data shows that tDCS-induced learning gains in our primary outcome variable (name recall accuracy) were maintained in older low learners for up to 3 months. In low performing young adults, decline rates were significantly higher for participants that had received sham compared to anodal tDCS during the training period. The more pronounced drop in performance in the low performing younger adults (drop in correct recall 24 hrs – 3 months f-u anodal/sham: 19.8±8.3/25.1±7.5) equals 26.8% (d'=.67). Figures are for illustrative purposes only. In the main results, we report baseline performance as a continuous variable.

Figure 1

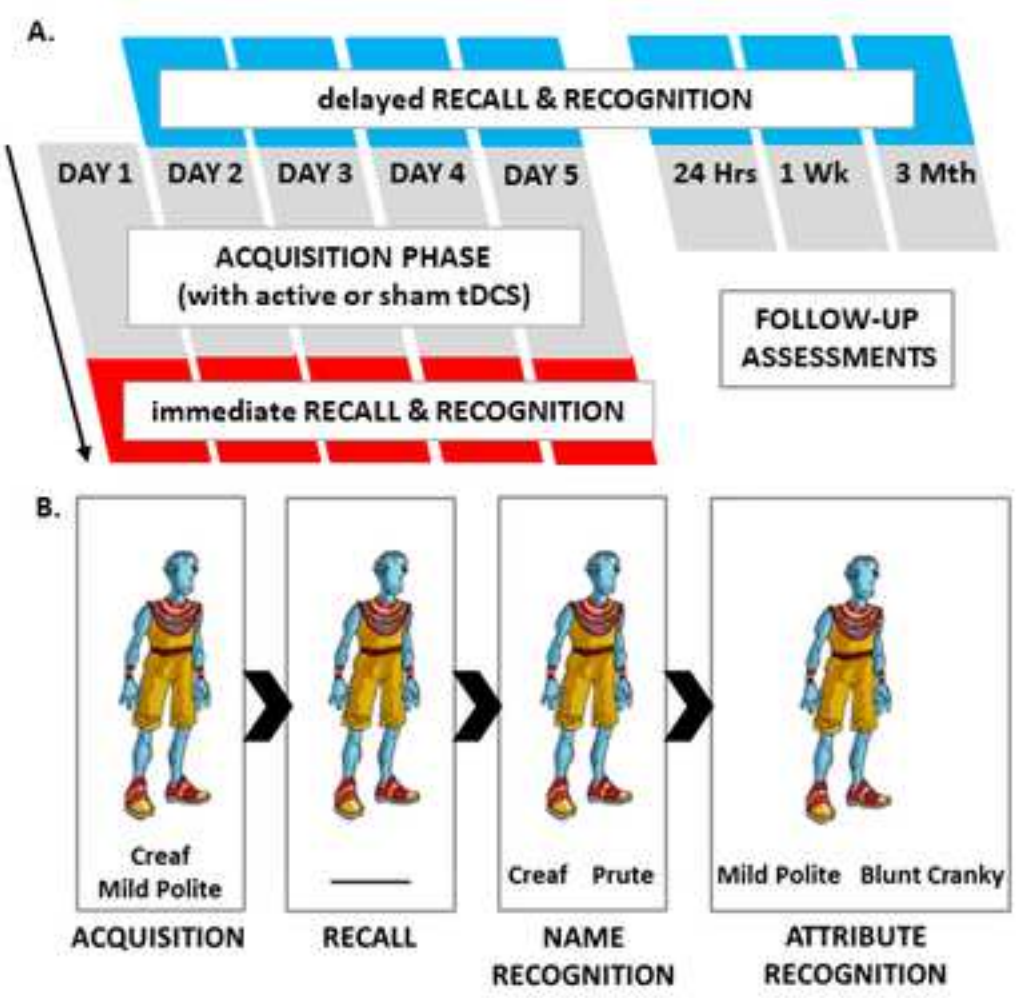


Figure 2

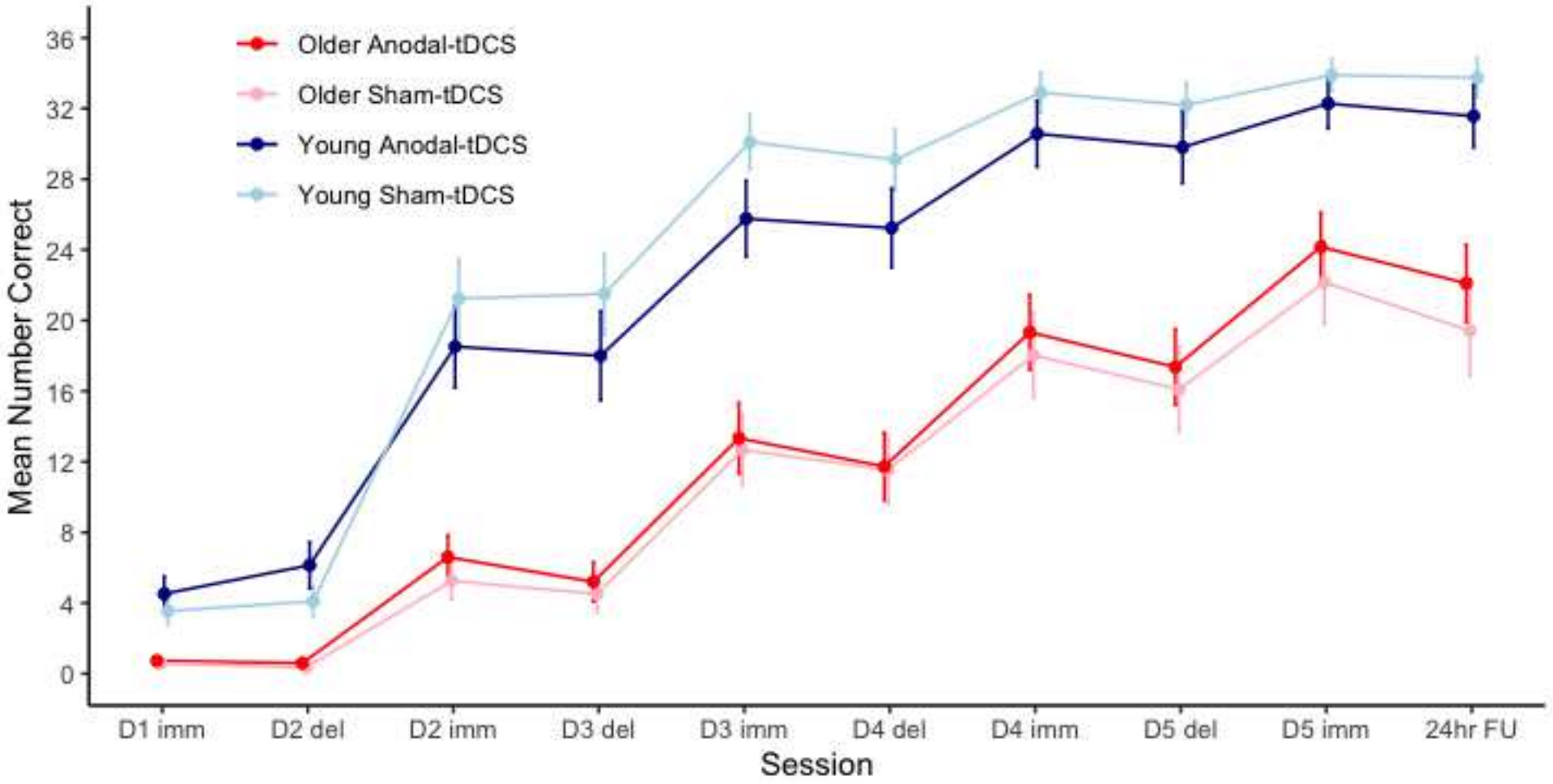


Figure 3

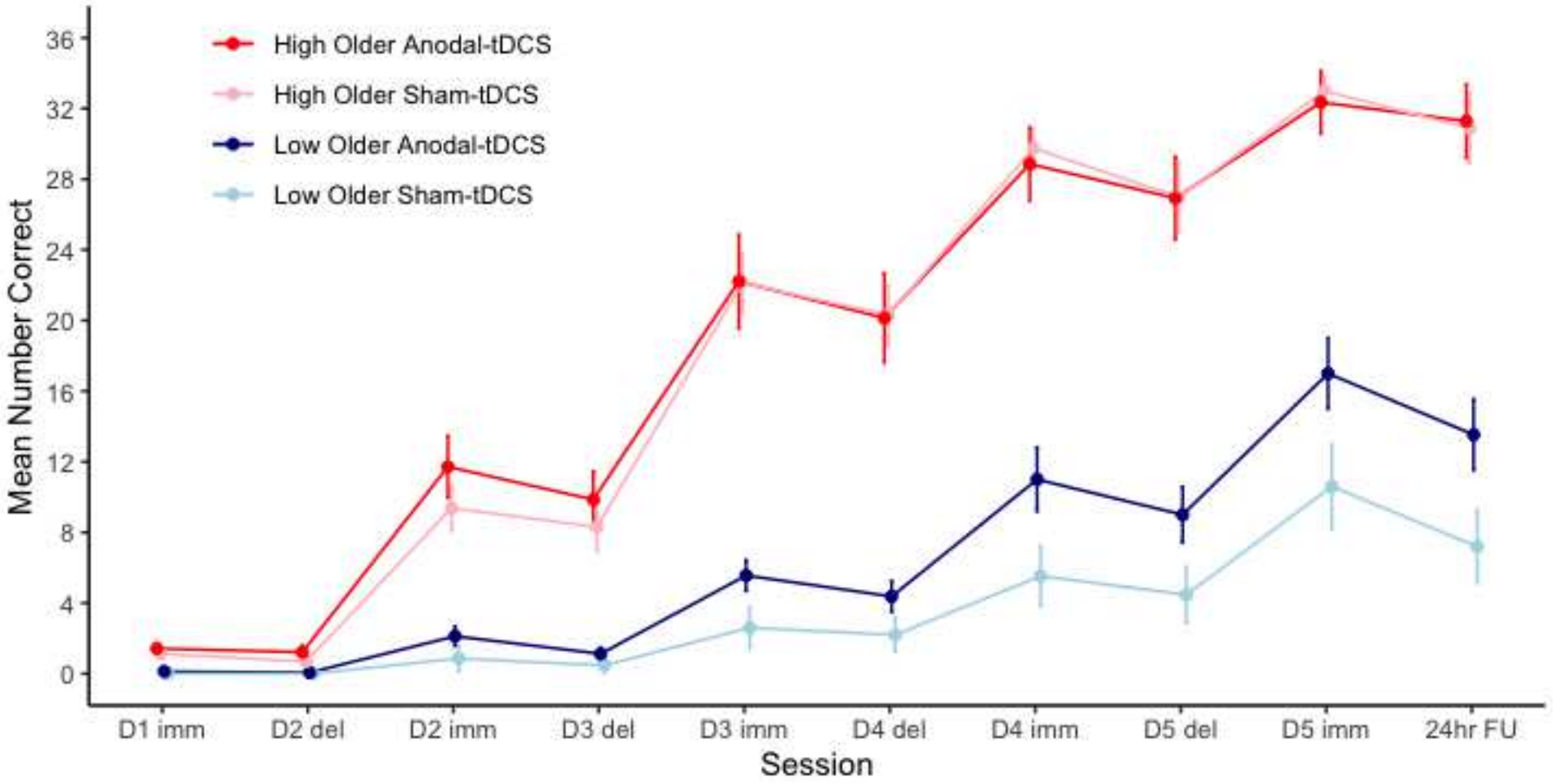
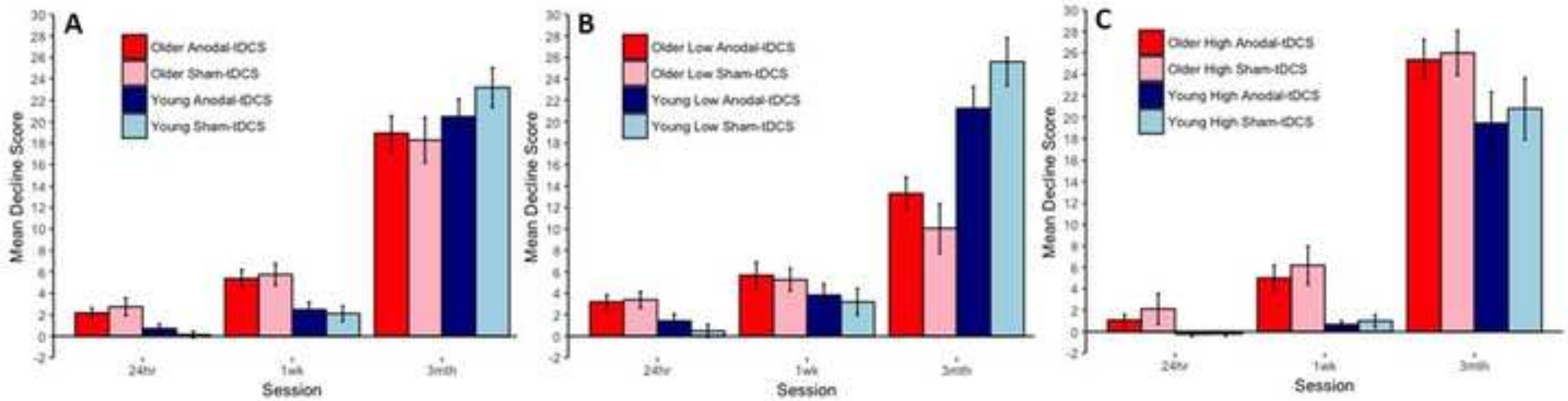


Figure 4

Click here to access/download;Figure;Figure_4_Follow-Up.jpg



Supplementary Tabe 1

Supplementary Tabe 2