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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

1   **Multisession transcranial direct current stimulation facilitates verbal learning**

2   **and memory consolidation in young and older adults**

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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.

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

61 studies that employed working memory training (Jones, Stephens, Alam, Bikson, & Berryhill, 2015;

62 Stephens & Berryhill, 2016) or other cognitive training paradigms (Antonenko et al., 2017; S. H. Park,

63 Seo, Kim, & Ko, 2014) have also demonstrated an improvement in specifically trained cognitive

64 functions and provided preliminary evidence for enhanced transfer effects to untrained cognitive

65 functions; but see Nilsson et al. (2017).

66 We expanded on these promising findings by training 101 healthy young and older adults on a verbal

67 associative learning paradigm in a prospective, double-blind, sham-tDCS controlled study to address

68 the following issues: (1) Because little is known about the time course of learning facilitation by

69 multi-session tDCS, this was investigated across multiple time points (i.e., daily during the training

70 period; 24 hrs, one week and three months later). (2) Multisession tDCS has been suggested to

71 specifically affect memory consolidation (Reis et al., 2015). However, this has only been

72 demonstrated in young individuals and by using procedural motor learning task. Here we probed

73 whether the same mechanism explains potential cognitive multisession tDCS effects in young and

74 older adults by investigating learning ability before and after each daily learning session. (3) Because

75 several previous cross-sectional tDCS studies have shown that baseline cognitive ability can affect

76 stimulation effectiveness (Berryhill & Jones, 2012; Learmonth, Thut, Benwell, & Harvey, 2015;

77 Meinzer, Lindenberg, Antonenko, Flaisch, & Flöel, 2013) we included this factor in our analyses. We

78 hypothesized that individuals with lower baseline ability would benefit most from the stimulation.

79 (4) Since some previous studies have suggested that multisession tDCS may enhance transfer to

80 untrained tasks (Antonenko et al., 2017; Cappelletti et al., 2013; S. H. Park et al., 2014), we

81 hypothesized that multisession tDCS would enhance transfer to tasks that share common cognitive

82 and neural components with the trained task (e.g., verbal learning or working memory).

83 **2. MATERIALS AND METHODS**

84 **2.1. Study overview:** The study employed a prospective, between-subjects, double-blind, placebo

85 ("sham-tDCS") controlled design and was conducted at the Centre for Clinical Research at the

86   University of Queensland. We employed an explicit learning paradigm where 41 younger adults, and

87   60 healthy older adults were trained to learn associations between pictures of "space alien"

88   characters (Gupta et al. 2004), their respective (non-word) names and two semantic attributes. The

89   training was administered across five consecutive days. Participants received either active (anodal-

90   tDCS) or placebo (sham-tDCS) stimulation of the left inferior frontal gyrus. IFG-tDCS was chosen,

91   because this montage has been shown to induce neural modulation in a larger fronto-temporal

92   network (Meinzer et al., 2012), overlapping with brain regions relevant for verbal associative

93   learning (Laine & Salmelin, 2010; Rodriguez-Fornells, Cunillera, Mestres-Misse, & de Diego-Balaguer,

94   2009).

95   Prior to the learning phase, all participants were assessed for baseline cognitive status and

96   completed a short version of the learning paradigm. Performance on the latter, along with age and

97   sex, was used to randomly assign participants to the stimulation groups (see below). Learned

98   associations were probed immediately prior to (except for day$_1$) and after each training day. This

99   allowed us to investigate both immediate and delayed effects of active tDCS. Maintenance of

100   learning success was assessed 24 hours, one week and three months after the end of the training.

101   Short- and long-term transfer effects to untrained cognitive functions were assessed using a

102   comprehensive and repeatable test battery. As baseline cognitive status predicted tDCS response in

103   previous studies, we also investigated whether baseline learning ability would mediate tDCS effects.

104   Blinding, adverse events and potential effects of tDCS on mood were systematically assessed. **Figure

105   1** illustrates the design of the study.

106   **2.2. Participants:** Participants were right-handed, healthy native English speakers from the Brisbane

107   metropolitan area (Young group: 25 women, 16 men, mean±SD years: 21.44±3.61; Older group: 50

108   women, 10 men, mean±SD years: 67.05±6.00). None had previously participated in a tDCS study.

109   Participants were excluded from the study according to standard tDCS safety criteria (e.g., if they

110   had a history of seizures, metallic objects in the head or cardiac pacemakers, current depression or

111   other psychiatric condition (Bikson et al., 2016)). None of the younger participants reported to be on

112   chronic medication, except for contraceptives (females). Several older participants reported to be on

113   chronic prescription medicine; however, medication status was comparable in the stimulation

114   groups (sham/anodal group: antihypertensives N=9/13, lipid lowering medication N=6/7,

115   antidiuretics N=2/3, antidiabetics n=2/1, thyroid hormone replacement N=3/6, COPD puffers:

116   N=1/1). None of the participants reported use of recreational drugs. All participants scored within

117   normal (age-corrected) ranges during baseline cognitive testing (**Table 1**). Within each age-group,

118   participants were pairwise stratified by age, sex and baseline learning ability on a short version of

119   the learning paradigm and randomly assigned to the stimulation groups. This procedure resulted in

120   two stimulation groups for each age group that were comparable regarding demographic

121   characteristics, baseline cognitive status and learning ability (**Table 1)**. Written informed consent

122   was obtained from each participant and the study was approved by the Human Research Ethics

123   Committee of The University of Queensland. Participants received AUD$250 upon study completion.

124   **2.3. Cognitive Screening:** To ensure normal cognitive function, all participants completed a

125   comprehensive neuropsychological test battery comprising tests used in the Australian Imaging,

126   Biomarker and Lifestyle Study of Ageing (Ellis et al., 2009) that are known to have good reliability

127   and validity. Tests covered a wide range of cognitive domains including language (vocabulary,

128   naming, and fluency), executive functions, visual-spatial processing, working memory and learning

129   (For details please see **Table 1**).

130   **2.4. Experimental learning paradigm:** We used an explicit verbal learning paradigm and participants

131   were trained to learn associations between "space aliens" (Gupta et al., 2004), a non-word "name"

132   and two semantic attributes. The training was administered across five consecutive weekdays (Mon-

133   Fri between 8 am - 4 pm, based on individual preferences but at the same time of day for individual

134   participants). Participants were instructed to memorize the names and attributes of each alien and

135   were informed that they would be tested using three memory tasks immediately after the training

136 (assessing *immediate after-effects* of tDCS) and prior to the start of the training session on the next

137 day (assessing *long-term after-effects*; from day_2 on, including the day after the training ended). Our

138 primary outcome measure was a *free recall task* that required written naming of each alien

139 character. Secondary outcome measures were two recognition tasks that required a forced-choice

140 decision between two non-word names (*name recognition*) or two sets of semantic attributes

141 (*attribute recognition task*). To assess *long-term maintenance* of potential tDCS effects, the recall

142 and recognition tasks were administered during two (one-week; three months) follow-up

143 assessments.

144 **2.4.1. Acquisition phase:** 36 color images of "space aliens" were used (see **Figure 1B** for an example,

145 (Gupta et al., 2004)). The aliens varied along three dimensions: head shape (human, N=12; vertically

146 elongated, N=12; horizontally elongated, N=12), number of arms (two, N=18; four, N=18), and type

147 of non-human appendage (tail, N=18; head appendage, N=18, (Gupta et al., 2004)). Each space alien

148 character was presented together with a non-word "name" (e.g., Prute) and two semantic attributes

149 (e.g., wise and heroic). 54 five-letter legal non-words were selected from the ARC Non-Word

150 Database (Rastle, Harrington, & Coltheart, 2002). 36 of these non-words served as the name for

151 each alien. 18 non-words were used as distractors in the forced-choice word recognition task (see

152 below). 108 English adjectives served as non-visual, semantic attributes (word length: 5-6 letters).

153 From this list, 54 pairs of adjectives were created so that both words matched for semantic

154 congruency (e.g., 'wise - heroic', rather than 'wise - stupid'). 36 of these attribute pairs served as the

155 attributes for each object. 18 pairs were used as distractors in the attribute recognition task (see

156 below). Semantic attributes were included because semantic information has been suggested to

157 facilitate learning (Angwin, Phua, & Copland, 2014).

158 The daily acquisition phase comprised 8 blocks with 9 trials in each block (in total 72 trials, with each

159 of the 36 alien, name and attribute combinations presented twice daily in a pseudo-randomised

160 order). Each trial began with a fixation cross presented in the centre of the screen for 1500 ms,

161 followed by the alien with its name and attributes for 8000 ms. Trials were separated by an interval

162 of 500 ms. Participants were instructed to learn the names and attributes of each alien and were

163 informed that they would subsequently be tested on their memory of these. During each block, the

164 aliens and their names and attributes were presented automatically on a computer screen with

165 white background. After each block, participants were prompted to take a short break and to press

166 "space" to resume.

167 **2.4.2. Recall and recognition tasks:** All participants completed three memory tasks immediately

168 after each training day, prior to the start of the next acquisition phase (from day2 on) and during the

169 three follow-up assessments (24 hrs, 1 week, 3 months). During the ***free recall task***, all aliens were

170 presented in random order on a white background and participants were instructed to use the

171 computer keyboard to type the name into a space provided on the display below the image.

172 Participants were instructed to type the whole name and to adhere to correct spelling. If they could

173 not recall the whole name, participants were told that they could type part of the name or to take a

174 guess at typing the whole name. If they were unable to produce a response, participants were

175 instructed to press "enter" to continue to the next trial. The number of phonetically similar

176 responses (e.g., "prute" rather than "proot") was very low (old adults: N=160 across all time points;

177 2.67/person, which is about 2% of approx. 8000 correct responses; young adults: N=51, 1.24/person,

178 approx. 0.46% of approx. 11.000 correct responses). Therefore, only full word responses with correct

179 spelling were scored as correct.

180 Afterwards, participants completed two forced-choice ***name*** and ***attribute recognition tasks***. Each

181 recognition task comprised 36 trials and the aliens were presented on a white background with a

182 selection of either two names or two attribute pairs at the bottom of the screen. Participants had to

183 select the correct name or attribute pair for each alien using the left or right mouse buttons. During

184 both recognition tasks, the distractors comprised 18 names or attributes assigned to other aliens

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

186 any of the tasks.

187 **2.5. Baseline learning ability:** A short version of the explicit learning paradigm (12 different alien,

188 word, attribute combinations) assessed baseline learning ability prior to the training. This short

189 version of the paradigm comprised three acquisition trials, each followed immediately by free recall

190 and name and attribute recognition trials. Learning success (# correctly recalled names) on this short

191 version was used together with age and sex to stratify participants to the intervention groups.

192 Although the stimulation groups did not differ in baseline learning ability (Younger: Sham, M=13.7,

193 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,

194 SD=4.44, p=0.71), older adults showed poorer baseline learning ability than younger adults

195 (p<0.001). Baseline learning ability was also considered in the statistical analysis (see below).

196 **2.6. Transfer effects:** To assess potential transfer effects to untrained cognitive functions, the

197 Cogstate computerized test battery (https://cogstate.com/) was administered immediately prior to

198 and after the training period, as well as during the two long-term follow-up assessments. The test

199 battery assessed a range of cognitive functions: processing speed, executive function, working

200 memory, and verbal, visuospatial, and associative learning. It was chosen because it is repeatable,

201 easy to administer, user-friendly, has good test-retest reliability(Cole et al., 2013), validity (Mielke et

202 al., 2015), and is sensitive to assess change in cognitive functions that decline with age and in age-

203 related cognitive disease (D. Darby, Maruff, Collie, & McStephen, 2002; D. G. Darby et al., 2012; Lim,

204 Ellis, et al., 2013; Lim, Jaeger, et al., 2013).

205 **2.7. Transcranial direct current stimulation:** tDCS was administered using a battery-driven direct

206 current stimulator (DC-Stimulator Plus, NeuroConn, Ilmenau, Germany). A pair of conductive rubber

207 electrodes inserted into saline-soaked sponge pockets were used and attached to the scalp using

208 rubber bands. The anode (5x7 cm²) was placed over the left inferior frontal gyrus (left IFG), an area

209 crucial for language learning (Rodriguez-Fornells et al., 2009). Moreover, because the left IFG is also

210   involved in a number of other cognitive processes like working memory (Nixon, Lazarova, Hodinott-

211   Hill, Gough, & Passingham, 2004) and semantic retrieval (Meinzer et al., 2009; Thompson-Schill,

212   D'Esposito, Aguirre, & Farah, 1997), we hypothesized that this montage would maximize both verbal

213   learning and potential transfer effects. The location of the left IFG was determined using the EEG

214   10-20 system as described previously (Meinzer et al., 2012; Meinzer et al., 2013). The cathode

215   (10x10 cm²) was placed over the contralateral supraorbital region. The large size of the reference

216   electrode renders the stimulation ineffective at this site without compromising the effect

217   underneath the anode (Nitsche et al., 2007). The current was ramped up immediately prior to the

218   acquisition phase over 10 seconds to 1 mA during both stimulation conditions. Afterwards, it

219   remained constant for 20 min (anodal tDCS) or 40 seconds (sham-tDCS) before ramping down (over

220   10 sec). This protocol allows effective blinding of participants in the sham-tDCS group by inducing a

221   similar physical sensation as in active stimulation without modulating neural activity (Gandiga,

222   Hummel, & Cohen, 2006; Gbadeyan, Steinhauser, McMahon, & Meinzer, 2016). TDCS was

223   administered during the acquisition phase (vs. retrieval phase) to maximize stimulation effects

224   (Simonsmeier, Grabner, Hein, Krenz, & Schneider, 2017). Investigator blinding was achieved by the

225   "study mode" of the DC stimulator where a predefined code triggered active or sham-tDCS. Codes

226   were assigned by a researcher not involved in conducting the experiments.

227   **2.8 Adverse effects and blinding:** Adverse effects were assessed using a self-report questionnaire

228   developed by Brunoni et al.(Brunoni et al., 2011). Participants rated the presence and intensity of a

229   range of possible adverse events (1=absent, 2=mild, 3=moderate, 4=severe, see **Tables 2 and 3**).

230   Participant blinding was assessed at the completion of training. Participants were asked the

231   following: "What type of stimulation do you believe you received? (a) real stimulation, (b) placebo,

232   or fake stimulation, or (c) unsure?"

233   **2.9. Statistical analysis:** Immediate and delayed effects of anodal-tDCS on recall and recognition

234   performance over the five days of training (# correct items) and at follow-up (change scores, e.g.,

235 Change$_{24}$=Day$_{5on}$-24-hrs) were analyzed using linear mixed effects models (Baayen, Davidson, &

236 Bates, 2008; Verbeke & Molenberghs, 2000) with the lme4 package (Version 1.1.12, (Bates, Mächler,

237 Bolker, & Walker, 2015)) in the R environment (Version 1.0.44; R Core Team 2014). Subject was

238 modelled as a random effect using random-intercept models. The five time-points for the learning

239 phase (TIME) for immediate effects of tDCS (i.e., after the end of each training session) were

240 modelled as fixed effects. The analysis of delayed effects (i.e., the next morning) across the training

241 phase comprised Days$_{2-5}$ and the short-term follow-up (24 hours). Long-term follow-up effects were

242 modelled separately based on change scores (e.g., Change$_{24}$=Day$_{5on}$-24-hrs) during the follow-up

243 time points (24 hrs, 1 week, 3 months). Transfer effects were analyzed with linear mixed effects

244 models for each Cogstate subtest by comparing pre-post training scores and scores across the three

245 follow-up time-points.

246 For immediate and long-term after-effects (i.e., after training vs. the next morning), follow-up, and

247 transfer data, the factors TIME, STIMULATION (anodal- vs. sham-tDCS), and AGEGROUP (young vs.

248 older) served as fixed effects. Baseline learning ability (BASELINE) was included as a continuous

249 covariate. The interactions TIME × STIMULATION assessed whether the slopes of the learning,

250 follow-up, and transfer task curves differed between the stimulation and age-groups. The TIME ×

251 STIMULATION × BASELINE interactions assessed whether baseline learning ability influenced these

252 effects. The TIME × STIMULATION × BASELINE × AGEGROUP interactions assessed for the impact of

253 both baseline learning and age-group on these effects. To assess between-group differences in

254 overnight memory decline across time, the same model was also used with change scores calculated

255 between immediate and long-term after-effects (e.g., Change$_1$=Day$_{1imm}$–Day$_{2long}$). P-values were

256 obtained using the Satterthwaite approximation to degrees of freedom via the lmerTest Package

257 (Version 2.0-33, (Kuznetsova, Brockhoff, & Christensen, 2015)). Unstandardized regression

258 coefficients (B), standard errors (SE), F values and significance levels are reported for all analyses.

259 Please note, because of the skewed sex distribution in our sample (75 women, 26 men), we also

260   conducted an exploratory analysis that included sex as an additional co-variate in the statistical

261   models. None of the significant effects were found to interact significantly with sex.

262   For display purposes, we also performed a hierarchical cluster analysis (Bailey, 1994) of the

263   continuous baseline learning data with a 2-cluster solution using Ward's method (Ward, 1963) to

264   generate a two-level categorical variable (Younger group: high learners, n=19; Anodal=9; low

265   learners, n=22; Anodal=12; Older group: high learners, n=30; Anodal=14; low learners, n=30;

266   Anodal=16). Figures relating to baseline learning illustrate data for these two subgroups. Detailed

267   information about demographic and neuropsychological profiles of the groups resulting from the 2-

268   cluster solution is provided in **Supplementary Tables 1+2.**

269   A 2x2 ANOVA (STIMULATION x AGEGROUP) assessed differences between the stimulation and age

270   groups on the neuropsychological test battery. Linear mixed models assessed differences in adverse

271   effects between stimulation and age groups over the five training days separately for each symptom.

272   STIMULATION, TIME (Day$_{1-5}$), and AGEGROUP were included in models as fixed effects. Blinding

273   success was evaluated using Chi^2-tests.

3. RESULTS

3.1. Baseline Cognitive Status, Adverse Effects, and Blinding

276   All participants performed within normal age ranges on the neuropsychological test battery. As

277   expected, older adults performed worse than younger adults on a number of tests (see **Table 1**).

278   Within each age-group, the two stimulation groups showed comparable neuropsychological profiles

279   (Note: a significant difference on the Trail Making Test A in the younger group did not survive

280   correcting for multiple comparisons). TDCS was well tolerated by participants of both age groups and

281   only mild adverse effects were reported. Across both age-groups, no differences in the degree of

282   reported adverse events in the two stimulation groups were found (all p's > 0.09, see **Tables 2 and**

283   **3**), except for tingling and scalp pain sensations: participants in the anodal group reported a greater

284 degree of tingling over time than sham (p=0.01), while participants in the sham group reported a

285 greater degree of (mild) scalp pain (p=0.03). Age effects were also observed: the younger group

286 reported a greater degree of headache, scalp pain, tingling, sleepiness and trouble concentrating

287 than the older adults (p<0.001-p=0.049). A greater decrease in the degree of itching sensations over

288 time was observed in the sham group, compared to anodal (p=0.02). Older adults in the anodal

289 group reported a greater degree of tingling than sham (p=0.03). Participant blinding was successful.

290 In the older group, only 23.3% of participants correctly guessed which type of stimulation they

291 received (Incorrect: 38.3%, Unsure: 38.3%). In the young group, 39% guessed correctly (Incorrect:

292 46.3%, Unsure: 14.6%). There were no differences between stimulation groups concerning blinding

293 results (Older: $\chi 2$ = 0.902, p = 0.637. Younger: $\chi 2$ = 0.75, p = 0.686).

294 **3.2. Learning Data**

295 **3.2.1. Overall Sample** (Young and Older Adults Combined)

296 First, we assessed immediate or delayed stimulation effects on learning rates over the five days of

297 training, and whether this was specific to age-group membership or baseline learning ability.

298 **3.2.2. Immediate after-effects of tDCS during the learning period** (Days$_{1-5}$, see **Figures 2 and 3**)

299 Participants successfully learned the novel active vocabulary (TIME, B = 8.00, SE = 1.01, F(1, 396)=

300 62.29, p<0.001). A significant TIME × STIMULATION × AGEGROUP × BASELINE interaction was

301 observed for the free-recall task (B = -0.30, SE = 1.14, F(1, 396) = 4.70, p=0.03), suggesting a specific

302 effect of stimulation dependent on age-group membership and baseline learning ability.

303 Subsequently, we performed two 3-way ANOVAs for each age group independently. A significant

304 TIME × STIMULATION × BASELINE interaction was identified in the older adults (B=-0.26, SE=0.09,

305 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).

306 To follow up on this interaction in older adults, we analysed the TIME × BASELINE interaction for

307 each stimulation group independently. This interaction was stronger for the sham group (TIME ×

308 BASELINE, $B = 0.64$, SE = 0.07, $F(1, 118)= 82.1$, p<0.001) than for the group that had received anodal

309 tDCS (TIME × BASELINE, $B = 0.38$, SE = 0.06, $F(1, 118)= 38.83$, p<0.001), suggesting that anodal tDCS

310 weakened the impact of baseline ability on recall immediately after the end of the training. This

311 means more pronounced benefits of anodal tDCS on learning ability were found specifically in

312 participants with lower baseline learning scores. This effect is illustrated in **Figure 3.**

313 **3.2.3. Long-term after-effects of tDCS during the learning period** (day$_2$-24 hour follow-up, see

314 **Figure 2 and 3**)

315 Recall performance as assessed prior to each training day improved across the training period (TIME,

316 $B = 7.59$, SE = 0.98, $F(1, 391.08)= 60.14$, p<0.001). A significant TIME × STIMULATION × AGEGROUP ×

317 BASELINE interaction was observed ($B = -0.32$, SE = 0.13, $F(1, 391.17) = 5.58$, p=0.02) for long-term

318 after-effects of tDCS on free-recall. Three-way ANOVAs were computed for each age group and a

319 significant TIME × STIMULATION × BASELINE interaction was identified in the older adults ($B = -0.31$,

320 SE = 0.09, $F(1, 231.11) = 10.89$, p<0.01), but not in the younger adults ($B = 0.01$, SE = 0.10, $F(1, 160)$

321 $= 0.02$, p=0.89). To follow-up this interaction in the older adults, we analysed the TIME × BASELINE

322 interaction for each stimulation group. The influence of this interaction was stronger for the sham

323 group (TIME × BASELINE, $B = 0.76$, SE = 0.07, $F(1, 114)= 109.04$, p<0.001), than for anodal (TIME ×

324 BASELINE, $B = 0.45$, SE = 0.06, $F(1, 117)= 61.33$, p<0.001), suggesting that anodal tDCS weakened the

325 impact of baseline ability on immediate learning. Therefore, stimulation also selectively improved

326 learning in older adults with lower baseline ability (see **Figure 3)**.

327 For the older adults, there was no difference between groups in overnight decline scores across time

328 (TIME × STIMULATION, $B=0.02$, SE=0.26, $F(1,231.51)=0.01$, p=0.93), indicating that the stimulation

329 effects were not selectively induced by effects on overnight consolidation. Baseline learning ability

330 did not further influence this null effect (TIME × STIMULATION × BASELINE, B=0.01, SE=0.05,

331 F(1,230.96)=0.09, p=0.77).

332 In summary, we show a facilitatory effect of anodal-tDCS on immediate learning for the free recall

333 task that is specific to older adults with lower baseline learning ability. These effects were

334 maintained during the testing session on the next day. Performance on the easier forced choice

335 name and attributed recognition tasks improved over time (all p's < 0.001), which demonstrates

336 participant motivation and task compliance. No further significant effects were found for these tasks

337 (see **Supplementary Table 1**).

338 **3.3. Long-term maintenance – Free recall task** (Day$_5$-3 month follow-up, see **Figure 4**)

339 During the learning phase, we observed age-related differences in stimulation response on the free-

340 recall task. Therefore, to assess long-term maintenance effects, we analysed recall accuracy decline

341 during the follow-up phase (24hrs, 1 week, 3 months) independently for young and older adults.

342 As expected, performance declined in both age groups during the three follow-up assessments (see

343 **Figure 4A**). In the older group, decline scores were comparable between the two stimulation groups

344 (TIME × STIMULATION, B = 0.57, SE = 1.51, F(1, 113.7) = 0.14, p=0.71), and baseline learning had no

345 effect (TIME × STIMULATION × BASELINE, B = -0.28, SE = 0.27, F(1, 113.1) = 1.12, p=0.29). This

346 suggests that stimulation-induced gains that were observed in older individuals with lower baseline

347 performance during the learning phase, were maintained during the follow-up.

348 In the young group, the rate of decline was greater for the sham group than for the anodal tDCS

349 group (TIME × STIMULATION, B = -7.78, SE = 3.41, F(1, 115) = 5.22, p=0.02). We also observed a

350 significant TIME × STIMULATION × BASELINE interaction (B = 0.46, SE = 0.23, F(1, 115) = 43.92,

351 p=0.049). Therefore, we inspected the effect of TIME × BASELINE in both stimulation conditions.

352 Neither sham nor anodal stimulation resulted in a significant TIME × BASELINE interaction. For Sham,

353 the TIME × BASELINE interaction was negative (B = -0.31, SE = 0.19, F(1, 56) = 2.49, p=0.12); for

354 anodal stimulation the TIME × BASELINE interaction was positive (B = 0.15, SE = 0.13, F(1, 59) = 1.35,

355 p=0.25). Therefore, stimulation differences were demonstrated at the level of the TIME ×

356   STIMULATION × BASELINE interaction, with anodal stimulation resulting in a greater effect of

357   baseline learning on decline over time. Overall, this suggests that even in the absence of immediate

358   stimulation effects on learning ability, learning gains were better maintained during the follow-up

359   assessments (i.e., 1 week, 3 months) in younger individuals with lower baseline learning scores who

360   had received anodal-tDCS (**Figure 4C**).

361   **3.4. Transfer effects**

362   No baseline differences were found between active and sham stimulation groups for any of the

363   Cogstate subtests (STIMULATION, all $p = 0.06 – 1.00$). Age-group membership had no further effect

364   (STIMULATION × AGEGROUP, all $p = 0.09 – 0.94$). There were some significant effects of stimulation

365   at different time points and for different tests (see **Tables 4 and 5**). However, none of them survived

366   correcting for multiple comparisons. Therefore, no substantial transfer effects were observed and

367   the stimulation groups were comparable in their performance across time on all Cogstate subtests

368   (TIME × STIMULATION, pre vs. post: $p = 0.02 – 0.93$; follow-up: $p = 0.01 – 0.95$). Including age-group

369   or baseline learning ability in the analysis did not further alter this outcome (TIME × STIMULATION ×

370   AGEGROUP, pre vs. post: $p = 0.04 – 0.92$; follow-up: $p = 0.01– 0.95$; TIME × STIMULATION ×

371   BASELINE, pre vs. post: $p = 0.04 – 0.97$; follow-up: $p = 0.01 – 0.92$).

372   **4. DISCUSSION**

373   This study demonstrated that multisession tDCS can improve verbal associative learning and its long-

374   term maintenance in healthy older adults. Importantly, beneficial tDCS effects were not exclusively

375   explained by overnight consolidation. In younger individuals, no immediate effects of tDCS were

376   found, but active tDCS reduced memory decline during the long-term follow-up sessions. In both

377   age-groups, beneficial effects of multisession tDCS were most pronounced in individuals with lower

378   baseline learning capacity. This shows that both short- and long-term tDCS effects are dependent on

379   baseline cognitive status. Our result thus emphasizes that tDCS is particularly suited to improve

380   learning and memory formation in those individuals who require such a "boost". However, it is

381   worth noting that multisession tDCS did not "restore" learning and memory in lower-functioning

382   (older) adults to the level of young individuals or high-functioning older participants. Blinding was

383   successful in both age-groups and only mild adverse effects were reported. Therefore, our study also

384   adds to the growing literature demonstrating that positive effects of multisession tDCS on brain

385   function can be achieved without side effects, making it an attractive tool for cognitive

386   enhancement in advanced age (Kortteenniemi, Ali-Sisto, Wikgren, & Lehto, 2017). Unlike previous

387   studies that reported near transfer effects to untrained materials (Antonenko et al., 2017; S. H. Park

388   et al., 2014), such effects were absent in the present study. This highlights a task-specific effect of

389   tDCS on brain activity elicited during learning and memory formation. Note that in a recent meta-

390   analysis by Nilsson et al. (2017) that failed to find beneficial effects of tDCS during cognitive training,

391   the outcome measures mixed transfer and training tasks, thus being uninformative of effects on

392   trained tasks.

393   Overall, young and older participants in both stimulation conditions showed evidence of learning

394   associations between the alien characters and their respective names and attributes across the five

395   training days, but there was also substantial variability in performance within each group.

396   Importantly, active tDCS selectively improved learning ability only in individuals with lower baseline

397   learning performance. Although potential tDCS effects in the high-performing subgroup may have

398   been masked by near ceiling effects on the two easier recognition tasks, learning curves were

399   comparable (in older adults almost identical) for active and sham-tDCS even for the more difficult

400   name recall task where there was a substantial room for improvement even in high performers.

401   These results suggest that baseline cognitive status is an important factor in determining stimulation

402   effectiveness (Silvanto, Muggleton, & Walsh, 2008). This is in line with previous cross-sectional

403   research showing that tDCS effects in elderly participants are modified by factors such as baseline

404   task performance and lateralization of brain activity (Berryhill & Jones, 2012; Learmonth et al., 2015;

405   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.,

432   2012). Moreover, only one recent study investigated the impact of multisession tDCS on learning

433   ability using an implicit object location learning paradigm (Antonenko et al., 2017). This study also

434   failed to find immediate stimulation effects on performance, which only became evident

435   immediately after a three-day training period, being maintained during a one month follow-up

436   assessment. It is worth noting that across the entire sample, tDCS did not result in immediate

437   performance improvement in the present study, and positive effects were limited to the subgroup of

438   low performers. As none of the previous multisession tDCS studies considered baseline cognitive

439   status or learning ability in their analysis, potential subgroup effects may have been missed.

440   Therefore, future studies are urgently needed to disentangle the contribution of chronological age,

441   target memory systems, and task characteristics on the temporal dynamics of multisession tDCS

442   response. Nonetheless, the results of our study did not provide support for the notion that tDCS

443   exclusively acts on memory consolidation mechanisms. This is also in line with a previous study from

444   our group that demonstrated immediate beneficial effects on verbal associative learning ability in

445   young participants (Meinzer, Jahnigen, et al., 2014). In contrast, no immediate effects were found in

446   the present younger sample, which is likely explained by the design of this study. Specifically, in an

447   attempt to keep the learning paradigm comparable for young and older adults and to account for

448   reduced learning ability in aging, the present study used relatively few picture-name pairs (N=36)

449   compared to our previous study (N=120; Meinzer et al. (2014)). Therefore, task demands were

450   substantially different. Nonetheless, beneficial long-term stimulation effects in the young group

451   were found (a) in those individuals that found the task "more challenging" (i.e., low performers) and

452   (b) during delayed memory retrieval (i.e., the follow-up assessments). Both findings are in line with a

453   task difficulty account that impacted multisession tDCS effects in the present study.

454   We also observed that tDCS-induced learning gains were largely maintained for up to three months

455   after the end of the training. This is in line with previous multisession tDCS studies in young adults

456   demonstrating long-term beneficial stimulation effects that outlasted the end of the training for at

457   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).

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696

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

698 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	

706

707

708 **Table 3.** Adverse effects reported by older participants in both stimulation groups (anodal-, sham-tDCS) as assessed after the end of each daily stimulation
709 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	

710

711

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

714 [1]Number of correct responses. [2]Number of errors. [3]Speed of performance (lower score = better performance). [4]Accuracy of performance (higher score =
715 better performance).

716 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 ×
717 StimGroup).

718 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-
719 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 ×
720 AgeGroup), [f]$p < 0.05$ (24 hours – 3 months, Time × StimGroup × Baseline), [g]$p < 0.01$ (24 hours – 3 months, Time × StimGroup × AgeGroup)

721

722

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

755   pronounced in the low performing older group that had received anodal tDCS. More pronounced

756   learning at the end of day 5 and the short-term follow up (24 hrs) amounted to 86.7% and 75.4%

757   respectively (Effect size d'=.64/.74; i.e., medium effect sizes). Please note, figures are for illustrative

758   purposes only. In the main results we report baseline performance as a continuous variable.

759

760   **Figure 4. Displays decline scores for correctly recalled names (# correct) for the follow-up time-**

761   **points relative to the end of the last training day.** (A) Entire sample, (B) participants with high or (C)

762   low learning ability during the baseline assessment. Data shows that tDCS-induced learning gains in

763   our primary outcome variable (name recall accuracy) were maintained in older low learners for up to

764   3 months. In low performing young adults, decline rates were significantly higher for participants

765   that had received sham compared to anodal tDCS during the training period. The more pronounced

766   drop in performance in the low performing younger adults (drop in correct recall 24 hrs – 3 months

767   f-u anodal/sham: 19.8±8.3/25.1±7.5) equals 26.8% (d'=.67). Figures are for illustrative purposes only.

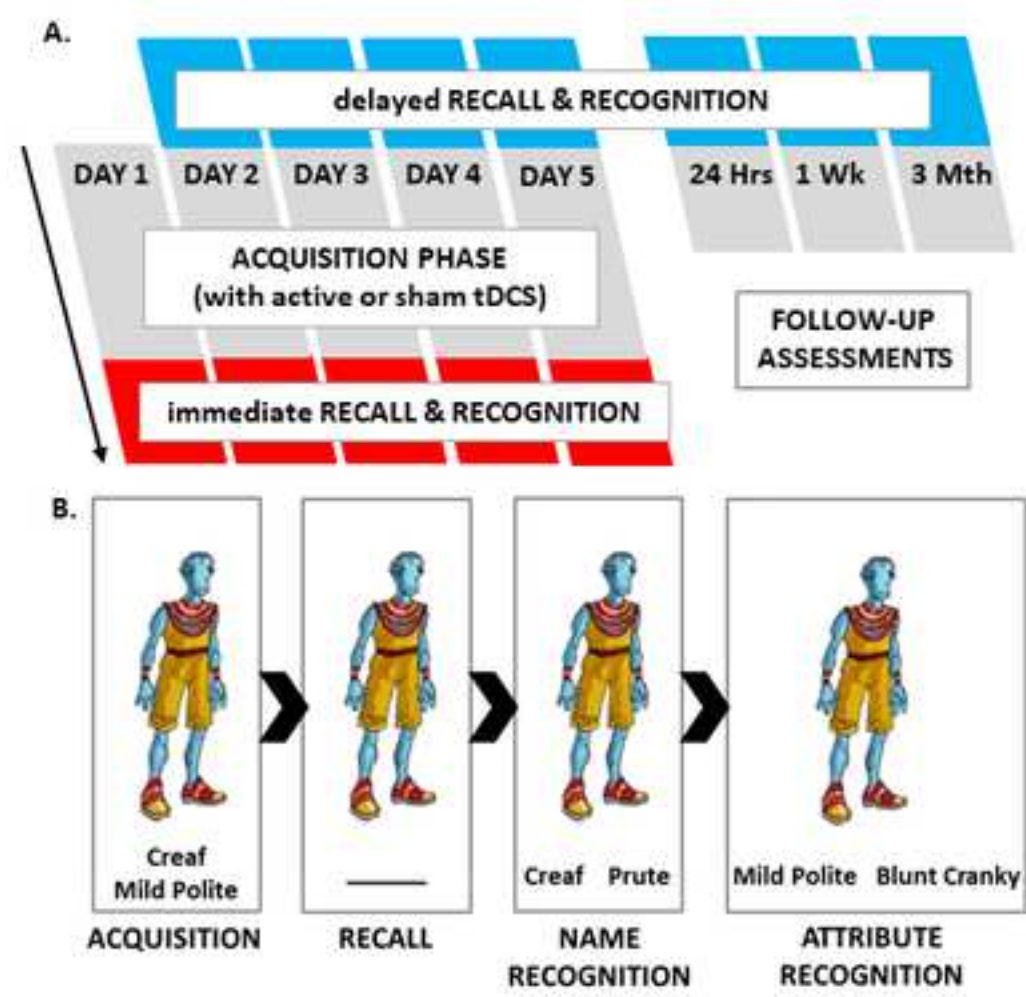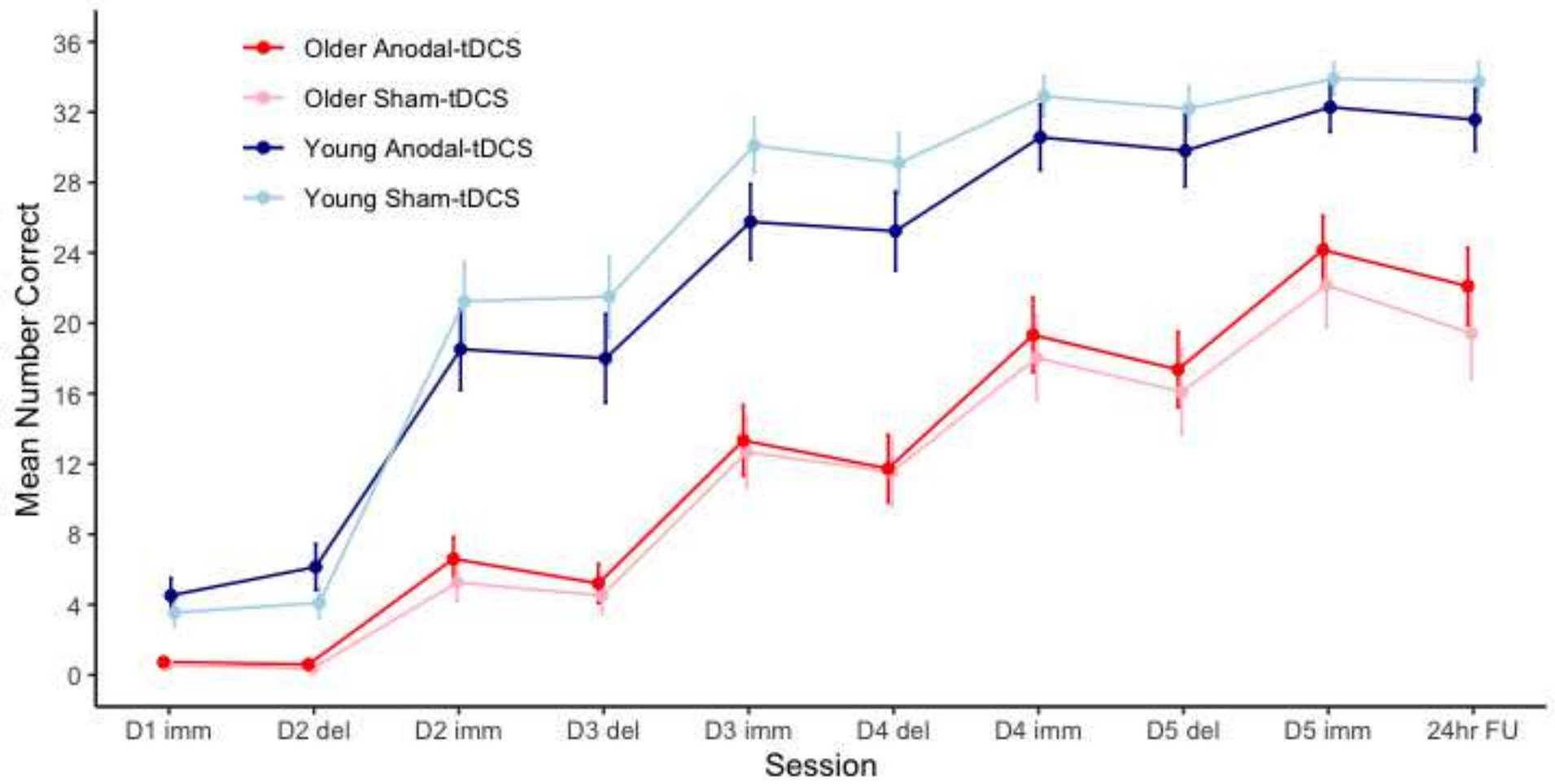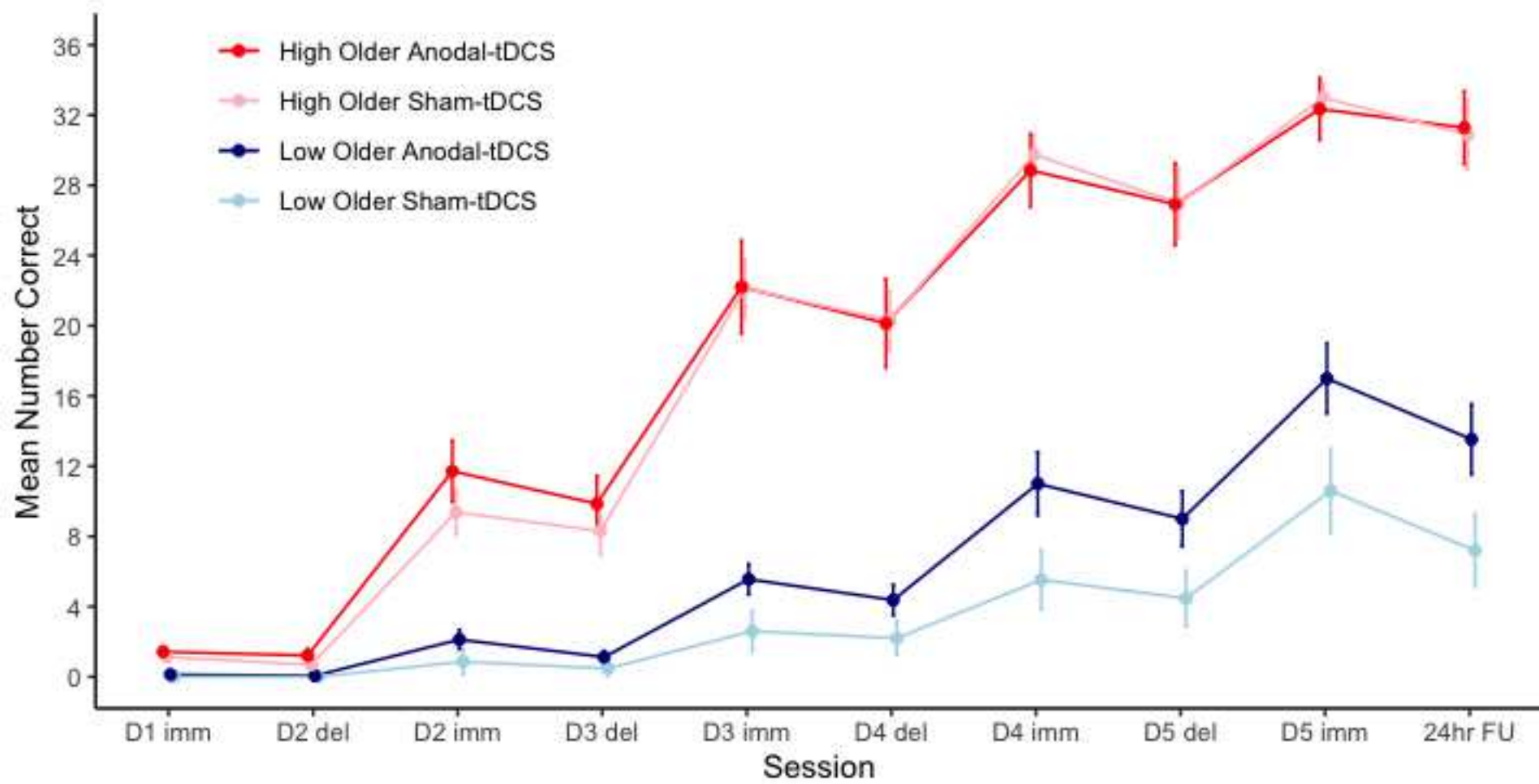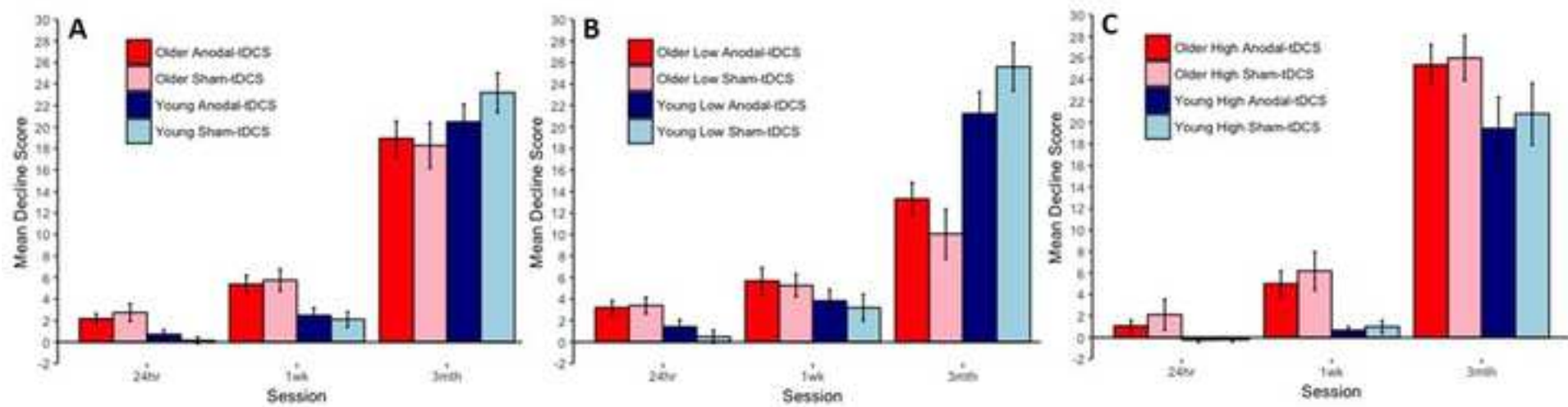768   In the main results, we report baseline performance as a continuous variable.

769

A.

delayed RECALL & RECOGNITION

DAY 1   DAY 2   DAY 3   DAY 4   DAY 5   24 Hrs   1 Wk   3 Mth

ACQUISITION PHASE
(with active or sham tDCS)

FOLLOW-UP
ASSESSMENTS

immediate RECALL & RECOGNITION

B.

Creaf
Mild Polite

Creaf   Prute

Mild Polite   Blunt Cranky

ACQUISITION   RECALL   NAME
RECOGNITION   ATTRIBUTE
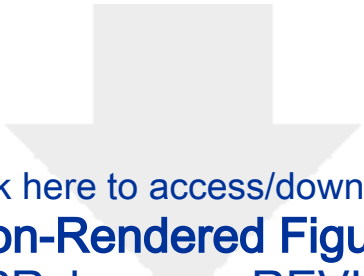RECOGNITION

Figure 2

Figure 3

Figure 4

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Table
Supplementary_Table_1_Perceval_Young_Group.docx

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Table
Supplementary_Table_2_Perceval_Older_Group.docx