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Evidence against benefits from cognitive training and transcranial direct current stimulation in healthy older adults

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Cognitive training and brain stimulation show promise for ameliorating age-related neurocognitive decline. However, evidence for this is controversial. In a Registered Report, we investigated the effects of these interventions, where 133 older adults were allocated to four groups (left prefrontal cortex anodal transcranial direct current stimulation (tDCS) with decision-making training, and three control groups) and trained over 5 days. They completed a task/questionnaire battery pre- and post-training, and at 1- and 3-month follow-ups. *COMT* and *BDNF* Val/Met polymorphisms were also assessed. Contrary to work in younger adults, there was evidence against tDCS-induced training enhancement on the decision-making task. Moreover, there was evidence against transfer of training gains to untrained tasks or everyday function measures at any post-intervention time points. As indicated by exploratory work, individual differences may have influenced outcomes. But, overall, the current decision-making training and tDCS protocol appears unlikely to lead to benefits for older adults.

The global population of older adults (>60 years) is expected to have more than doubled by 2050 (ref. [1]). Subsequent increases in age-related disease and disability will create substantial economic and social challenges worldwide[2]. For instance, individuals will need to remain in the workforce for longer despite age-related health changes and decreased functional capacity, and there will be increased pressure placed on health care systems[3]. Neurocognitive decline is arguably one of the most debilitating age-related health changes[4], affecting up to 30% of adults over 65 years of age[5], and increasing the risk of progression to dementia[4]. Specific cognitive abilities categorized as 'executive functions', are disproportionately represented in this decline[4,6,7] and include, but are not limited to attentional control, working memory, inhibition, and cognitive flexibility[8]. Involved in processes such as planning, decision-making and problem solving, executive functions are crucial to participation in activities of daily living[9] (ADLs) and are highly predictive of functional independence[10]. Therefore, age-related decline in executive function is undoubtedly one of the key challenges posed by this demographic shift.

Much excitement has been generated, in both the research community and general public, regarding the promise of cognitive training and brain stimulation to ameliorate age-related neurocognitive decline[11]. Indeed, several studies have attempted to slow or reverse such decline using cognitive training and/or non-invasive brain stimulation techniques such as transcranial direct current stimulation[12,13] (tDCS). In particular, anodal tDCS combined with effective training paradigms has yielded performance enhancements on various trained tasks, above those of training alone[14–17]. Critically, such effects have been demonstrated with older adult populations in cognitive abilities such as language[18], multitasking[19] and error awareness[20]. There has been comparatively less research on the possibility of transfer of benefits across cognitive domains, and the research that does exist on this issue is controversial. The available evidence suggests protocols that combine tDCS and training approaches appear most likely to generate sustainable transfer, for example[12,13,21].

A characteristic common across tDCS and training research is that much of the work is limited by poorly controlled experimental protocols, small sample sizes and short follow-up testing periods (which fail to fully assess the sustained impact of any observed enhancements). For example, most studies rely solely on a sham tDCS control condition to account for placebo effects of stimulation, thus assuming that sham and active tDCS are indistinguishable to the participant[22]. But, whilst participants may not consciously distinguish between active and sham tDCS, there could be differences in other factors such as arousal[23,24]. As such, it is necessary that studies include additional control conditions, such as alternative electrode locations that do not overlap with targeted brain regions of interest[25]. Attesting to these methodological issues, recent meta-analyses have yielded conflicting results regarding the utility of tDCS in augmenting cognitive training benefits[26,27]. Also noteworthy is that most studies have evaluated the influence of combined tDCS and training on working memory outcomes. Consequently, to date, there has been minimal research on combined stimulation and training of other executive functions that might also have a meaningful impact on an individual's functional capacity and well-being. Added to these issues is the fact that few tDCS and/or training studies have been pre-registered. Thus, publication bias may have had an influence on the reported findings in this field[28]. This is particularly concerning as brain training and stimulation protocols are gaining popular interest within the general community[29].

One possible alternative to working memory approaches is a combined training and stimulation protocol recently developed by our group[21]. In our study, healthy younger adult participants received concurrent training on a speeded decision-making task, while receiving anodal tDCS over the left prefrontal cortex (PFC).

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Following training and stimulation, participants were quicker at executing decisions, and also became more efficient at visual search, which was included as an unrelated (transfer) attentional task. These benefits were found to be above those of training alone, or of cathodal stimulation paired with training, and were specific to left PFC stimulation. Given this tightly controlled experimental design (cathodal, sham and alternative electrode location control conditions), these findings suggest that training benefits on a decision-making task are indeed enhanced by tDCS, and hint at the potential utility of this protocol for producing generalized executive function benefits. Importantly, Filmer et al.[21] considered the visual search task a measure of far transfer, as it involved stimuli presented in a different sensory modality to the trained task (visual versus auditory), required a different type of behavioural task (finding a stimulus amongst spatially arranged distractors versus selecting the correct response to a presented stimulus) and drew on a distinct psychological operation (spatial attention). It is therefore plausible that decision-making training when paired with anodal tDCS, as in the Filmer et al. study[21], might elicit generalized improvements across other cognitive domains, particularly other executive functions. This effect is yet to be investigated within an older adult population, and on a wider range of tasks, highlighting a promising avenue for future research.

The current project employed a similar protocol to Filmer et al.[21], to evaluate whether combined decision-making training and anodal tDCS is effective in producing lasting and generalizable executive function benefits, in the largest cohort of healthy older adults of any investigation conducted to date. Improving on existing research, we administered several control conditions to determine whether combined decision-making training and tDCS over the left PFC is more effective than decision-making training alone, and whether training and stimulation effects are specific to the decision-making task, and the left PFC electrode location. We assessed participants at several time points on a wide range of near and far transfer measures of executive function. Specifically, we employed six executive function tasks, two ecologically valid self- and informant-report questionnaires assessing everyday functioning, two episodic memory tasks and two control processing-speed tasks. We have focused on executive functions in particular, as some of the most debilitating age-related cognitive impairments are those in this domain, given their association with independent living and a variety of everyday behaviours[9,10]. We also recognize that there is considerable public interest in the possibility of memory enhancement through tDCS, due to age-related decline in episodic memory, and increasing concerns about dementia. Thus, we also included two episodic memory tasks, to examine the utility of our protocol for improving long-term memory in older adults, and to determine whether any training and stimulation benefits extended beyond executive functions.

This study adheres to the Registered Report format, thus ensuring the integrity of methodology and results, and preventing potential publication bias. By following a rigorous experimental design, with adequate control conditions and an extensive battery of transfer tasks, the current research yields important new insights into a critical research question: Can combined cognitive training and tDCS provide generalizable cognitive function benefits in older adults, particularly executive functions? Critically, we predicted far transfer gains at 1 month post-intervention, and based all sampling decisions on this hypothesis test. We also predicted training and stimulation-related improvement on a range of near, far and translational tasks, and two ecologically valid measures of everyday functioning, but not on memory or control tasks.

Results

The present study investigated the utility of a combined decision-making training and tDCS protocol in healthy older adults, aged 60–75 years, where 133 participants were allocated pseudorandomly to one of four stratified groups (based on age, gender, education and physical activity) to receive: (1) training and concurrent anodal tDCS over the left PFC, (2) combined training and concurrent sham tDCS over the left PFC, (3) combined training and concurrent anodal tDCS over the visual cortex (V1) and (4) combined control training (a basic visual attention task as 'placebo' training) and concurrent anodal tDCS over the left PFC. A Consolidated Standards of Reporting Trials (CONSORT) flow diagram is presented in Fig. 1. Training and/or stimulation were administered for five consecutive days, and participants were repeatedly assessed on a large battery of cognitive tasks and questionnaires (including reports from a significant other) immediately pre- and 1 day post-intervention, and at 1- and 3-month follow-ups. *COMT* and *BDNF* genetic polymorphisms were obtained as individual difference variables. Bayesian analysis approaches were employed to assess the evidence for or against a group × time interaction on each of the cognitive tasks and questionnaires at each post-intervention time point, and on the decision-making task across each training session.

Overview. As per the Bayesian sampling approach, we selected a critical hypothesis test to be used in decisions relating to data collection (that is, when to stop collecting data), namely the effect of training and stimulation on far transfer performance (including visual search reaction time, Operation-Span Working Memory Task (OSpan) score and stop-signal reaction time (SSRT)) at 1-month follow-up. We predicted that participants who received combined training and anodal tDCS would display greater improvement on far transfer tasks at 1-month follow-up, specifically for the left PFC electrode site, than those who received training alone or stimulation and training on a control task. Improvement would be reflected as a decrease in visual search reaction time and SSRT, and an increase in OSpan score. Later referred to as hypothesis 1, we chose this test as we were particularly interested in whether our protocol could induce far transfer performance benefits that persisted over time, and believed the presence of such benefits at 1 month post-intervention would be a meaningful result with considerable practical implications. Therefore, our main outcome parameter was far transfer performance. We were also interested in the effect of training and stimulation on the training task, each of the transfer tasks, and the questionnaires, and whether group differences in performance change were evident up to 3 months post-intervention. Accordingly, hypothesis 2 predicted that participants who received combined training and tDCS over the left PFC would display better performance than those in control conditions, on all executive function outcome measures across all post-intervention time points, but not on memory tasks or processing-speed control tasks. For executive function tasks, better performance is indicated by shorter reaction times or reaction time costs for the decision-making and single versus dual tasks, respectively, decreased number of errors on the Wisconsin Card Sorting Test (WCST) and increased accuracy on the Reading the Mind in the Eyes Test (RMET). For questionnaire measures, better outcomes are reflected by a smaller Behavior Rating Inventory of Executive Function - Adult (BRIEF-A) Global Executive Composite (self and informant scores) and higher Frenchay Activities Index (FAI) score (self and informant scores). We also wished to evaluate the trajectory of any training and tDCS benefits across each stimulation session. Hypothesis 3 predicted that between-group differences would be evident from the second stimulation session, such that the combined training + left PFC tDCS group would display greater improvement in performance on the training task (that is, decreased reaction times) than control groups, and that this pattern of results would persist and increase throughout the following stimulation sessions. Finally, for both *COMT* and *BDNF* genes we evaluated the influence of genotype on baseline performance on all tasks (see specific measures in Methods) and whether there was a differential effect of training and stimulation

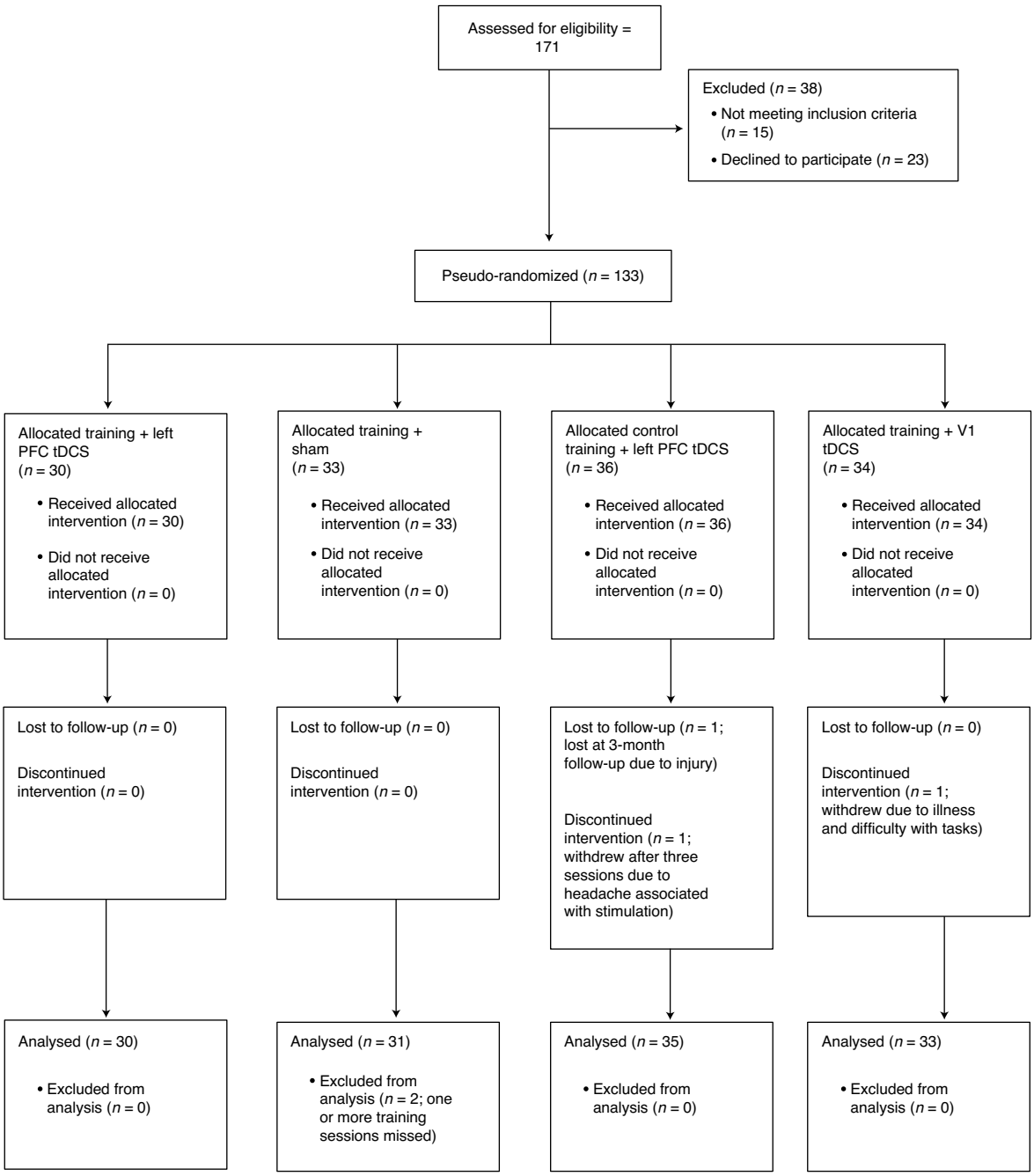

Fig. 1 | CONSORT diagram. Flow diagram outlining the progress of all participants through the study.

for each genotype. Hypothesis 4 predicted that genotype would have an influence on response to tDCS and training. However, due to limited data on this topic, and the mixed outcomes of relevant published research, we did not specify the direction of any effect. Hypotheses 2–4 were tested in addition to the critical hypothesis test, but did not contribute to data collection decisions.

We adopted a Bayesian approach to evaluate relative support from the data for and against null and alternative hypotheses[30]. This included: (1) separate two-way (group × time) Bayesian repeated-measures ANOVAs for each task/questionnaire, for each post-intervention time point and each stimulation session for the training task only, (2) Bayesian independent samples *t* tests (two-tailed) on pre–post difference scores, for each of the tasks and time points where a significant interaction was found at step 1, (3) a Bayesian one-way ANOVA on pre-intervention performance, to check for between-group baseline differences, (4) separate Bayesian one-way ANOVAs on baseline performance for each task and gene (*COMT* and *BDNF*), (5) separate Bayesian repeated-measures ANOVAs for each training and far transfer task and gene group (*COMT*/*BDNF*), at each post-intervention time point and (6) Bayesian two-way ANOVAs on difference scores, for each task and time point where a significant three-way interaction was found at step 5, with genotypes included in a pairwise manner (that is, Val/Val and Val/Met, Val/Val and Met/Met, and Val/Met and Met/Met).

All registered analyses were conducted in JASP (JASP Team, 2016) using zero-centred Cauchy priors[31], placing greater mass on large effects than the standard normal distribution, and favouring the null more than other models[32]. Our analyses closely followed the registered plan, but we also employed a new feature in JASP, which provides relative evidence for the inclusion of each factor in

Table 1 | Descriptive statistics for the trained task and all transfer tasks

	Pre-intervention				1 day post-intervention				1-month follow-up				3-month follow-up			
Task	**Train + left PFC tDCS**	**Train + sham**	**Control train + left PFC tDCS**	**Train + V1 tDCS**	**Train + left PFC tDCS**	**Train + sham**	**Control train + left PFC tDCS**	**Train + V1 tDCS**	**Train + left PFC tDCS**	**Train + sham**	**Control train + left PFC tDCS**	**Train + V1 tDCS**	**Train + left PFC tDCS**	**Train + sham**	**Control train + left PFC tDCS**	**Train + V1 tDCS**
Decision-making RT (ms)	1,094.22 (109.66)	1,118.94 (85.833)	1,078.37 (120.20)	1,066.42 (104.30)	972.15 (100.36)	975.52 (110.94)	1,017.51 (127.05)	961.99 (124.78)	994.86 (107.08)	1,003.99 (111.48)	1,029.37 (119.20)	985.11 (114.54)	1,006.32 (106.80)	1,021.18 (103.58)	1,018.06 (116.36)	1,005.93 (99.86)
Single versus dual task (ms)	639.93 (233.32)	575.22 (221.29)	554.15 (359.04)	603.13 (277.81)	678.858 (177.58)	578.88 (257.93)	653.02 (193.86)	603.96 (223.96)	696.82 (180.49)	636.95 (292.10)	631.19 (160.31)	652.07 (226.48)	676.82 (230.48)	634.67 (278.22)	633.90 (171.22)	587.42 (255.62)
Visual search SS12 – SS8 (ms)	396.28 (171.21)	391.18 (161.06)	377.52 (151.36)	372.84 (141.75)	338.88 (136.36)	316.77 (155.58)	320.90 (91.89)	289.59 (101.33)	283.82 (102.55)	294.60 (127.27)	310.8 (120.55)	291.56 (140.22)	299.50 (107.14)	285.03 (120.96)	298.25 (102.23)	285.70 (107.97)
OSpan total score	6.47 (2.74)	5.84 (3.31)	5.60 (3.55)	5.58 (2.63)	7.63 (3.12)	7.19 (3.66)	7.0 (3.46)	6.67 (2.88)	7.77 (3.12)	6.81 (3.57)	6.31 (3.15)	7.06 (2.87)	8.1 (2.78)	6.29 (2.96)	6.59 (3.48)	6.91 (2.72)
Stop-signal reaction time (ms)	230.79 (120.96)	272.39 (127.61)	225.31 (144.26)	282.06 (161.19)	116.93 (175.75)	192.86 (177.46)	119.60 (182.89)	177.41 (174.02)	39.52 (154.24)	137.04 (215.27)	149.70 (286.59)	126.14 (173.06)	83.18 (189.38)	76.44 (175.95)	93.30 (181.48)	93.36 (170.43)
RMET (% correct)	69.35 (12.34)	69.82 (11.03)	72.06 (11.60)	68.35 (12.30)	68.33 (11.53)	71.94 (11.95)	69.68 (11.44)	65.40 (14.77)	71.30 (8.46)	73.33 (13.14)	71.75 (12.04)	70.40 (13.67)	69.72 (13.26)	73.06 (12.23)	71.57 (12.48)	71.44 (11.03)
WCST (% errors standard score)	110.6 (13.81)	108.8 (15.97)	106.77 (24.62)	103.82 (13.0)	120.33 (16.75)	120.07 (16.01)	119.03 (15.89)	114.91 (16.34)	120.4 (15.46)	121.36 (15.03)	119.41 (15.29)	117.12 (13.57)	120.5 (16.07)	121.94 (18.41)	120.65 (16.43)	120.49 (13.44)
Verbal memory task (% correct)	83.19 (13.77)	85.10 (10.57)	86.35 (9.75)	86.47 (10.30)	85.45 (11.39)	85.16 (10.20)	87.31 (8.42)	87.70 (10.21)	90.73 (10.19)	88.27 (12.36)	90.82 (7.80)	89.70 (11.13)	90.07 (10.38)	88.00 (10.07)	88.06 (10.64)	88.84 (10.74)
Visual memory task (% correct)	94.07 (5.34)	95.16 (5.36)	94.80 (3.89)	93.81 (6.39)	96.66 (3.06)	95.29 (5.88)	96.23 (3.17)	94.85 (5.87)	97.45 (2.97)	97.73 (2.50)	97.83 (2.40)	96.55 (3.51)	98.00 (2.73)	96.71 (5.13)	97.59 (1.96)	96.67 (4.46)
Stimulus detection (ms)	307.86 (28.80)	312.32 (36.04)	309.71 (32.09)	298.21 (29.42)	308.86 (39.19)	304.49 (41.28)	306.71 (30.46)	299.09 (30.29)	310.90 (29.72)	317.79 (50.33)	309.69 (28.58)	303.98 (36.92)	311.09 (29.85)	314.68 (39.41)	312.09 (36.41)	301.02 (36.16)
Symbol-digit modalities (total correct)	35.47 (6.76)	33.97 (8.19)	36.38 (7.19)	35.55 (5.79)	40.8 (7.86)	38.71 (6.9)	41.94 (7.92)	39.39 (6.18)	40.67 (7.76)	39.81 (7.55)	41.62 (8.05)	38.64 (5.57)	42.0 (7.16)	39.29 (7.46)	41.35 (8.09)	38.97 (5.54)
BRIEF-A self report (T score)	52.3 (12.09)	50.167 (8.27)	51.83 (13.50)	50.52 (7.91)	50.43 (13.72)	48.16 (9.29)	50.49 (14.74)	49.36 (9.02)	47.2 (8.62)	47.84 (8.85)	49.89 (14.00)	50.18 (9.17)	46.67 (8.93)	47.52 (8.93)	49.91 (14.55)	48.06 (7.87)
BRIEF-A informant report (T score)	47.96 (8.01)	47.67 (7.91)	48.18 (7.38)	49.00 (6.99)	48.24 (8.50)	46.77 (7.56)	46.844 (7.08)	47.04 (7.14)	47.31 (8.59)	46.38 (9.06)	46.63 (7.15)	47.32 (7.58)	47.71 (8.81)	45.33 (7.36)	45.93 (8.58)	47.8 (7.43)
FAI total: self report	36.97 (3.65)	35.36 (6.82)	35.77 (4.4)	36.69 (3.53)	36.87 (3.89)	34.94 (7.05)	35.82 (3.78)	36.16 (4.28)	37.33 (3.02)	35.03 (5.82)	36.43 (3.98)	36.27 (3.96)	37.27 (3.70)	35.833 (4.04)	36.10 (3.98)	36.46 (3.83)
FAI total: informant report	35.57 (3.48)	35.57 (5.05)	35.00 (4.96)	35.50 (3.68)	35.13 (4.26)	35.41 (5.5)	34.9 (5.04)	35.69 (3.93)	36.13 (4.36)	35.76 (5.71)	34.67 (5.87)	34.96 (4.96)	36.22 (5.12)	35.5 (5.61)	35.82 (4.62)	35.4 (4.82)

Note: Standard deviations presented in parenthesis.

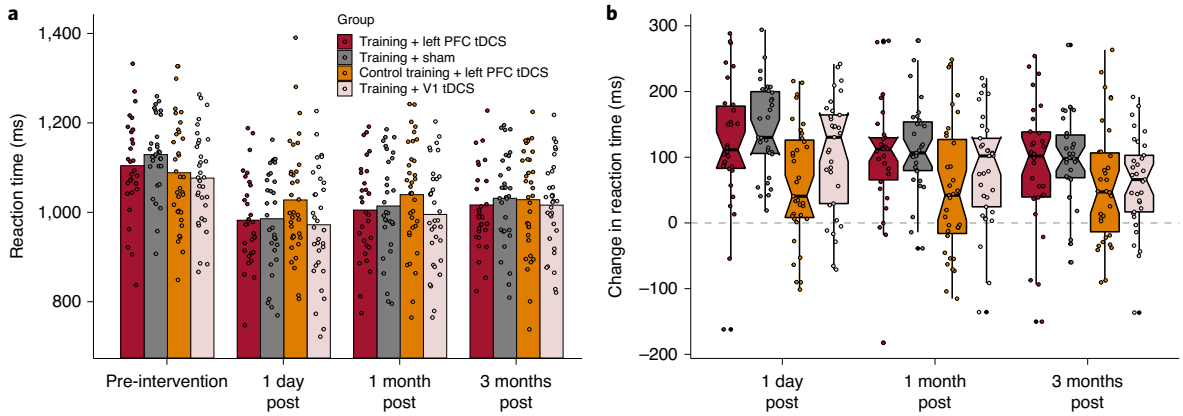

Fig. 2 | Decision-making task performance. a, Barplots depicting mean reaction time on the decision-making task for each group at each time point. Individual data points are superimposed on bars. **b**, Notched boxplots with quartile ranges and medians depict reaction time change scores for the decision-making task, at each post-intervention time point relative to baseline. Individual change scores are superimposed on each boxplot.

the model (that is, main effects and interactions) across matched models, and provides a simpler method of interpreting interaction effects. We report this 'BF_{inc}' value for all interaction effects. Bayesian one-way ANOVAs and pairwise statistics are reported as BF_{10} as these are equivalent to BF_{inc} in simpler analyses. Exploratory analyses were conducted in JASP and R.

Registered analyses. Descriptive statistics for the decision-making trained task and all transfer tasks are presented in Table 1.

Decision-making (trained) task. Performance on the decision-making task for each group at each time point is depicted in Fig. 2a. Critically, there was moderate evidence against between-group differences in performance at baseline ($BF_{10} = 0.26$, $\eta^2 = 0.034$), suggesting that our groups were well matched. A Bayesian repeated-measures ANOVA on decision-making task performance at pre- and 1 day post-intervention, revealed strong evidence for a main effect of time ($BF_{inc} = 3.10 \times e^{22}$, $\eta_p^2 = 0.615$), reflecting faster reaction times at 1 day post-intervention. There was moderate evidence against a main effect of group ($BF_{inc} = 0.22$, $\eta_p^2 = 0.018$), but strong evidence for a group × time interaction ($BF_{inc} = 22.15$, $\eta_p^2 = 0.116$). Follow-up analyses of difference scores (Fig. 2b) indicated moderate evidence for a training effect when comparing the training + left PFC tDCS group with the control training + left PFC tDCS group ($BF_{10} = 4.68$, $d = 0.662$). But, we also compared all three trained groups together versus the control training group and found strong evidence for a training effect ($BF_{10} = 59.78$, $d = 0.715$). In contrast to findings in younger adults[21], there was anecdotal evidence against differences in performance change between the training + left PFC tDCS group relative to training + sham ($BF_{10} = 0.39$, $d = -0.252$) or training + V1 tDCS ($BF_{10} = 0.33$, $d = 0.190$), thus it is unclear whether left PFC tDCS enhanced training benefits on the decision-making task. Bayesian repeated-measures ANOVAs at both follow-up time points revealed strong evidence for a main effect of time ($BF_{inc} = 4.44 \times e^{16}$, $\eta_p^2 = 0.507$; $BF_{inc} = 1.47 \times e^{15}$, $\eta_p^2 = 0.468$ at 1- and 3-month follow-up, respectively), again reflecting a decrease in reaction times relative to baseline. There was moderate evidence against an effect of group at 1- and 3-month follow-up ($BF_{inc} = 0.22$, $\eta_p^2 = 0.018$; $BF_{inc} = 0.21$, $\eta_p^2 = 0.016$). Similarly, there was anecdotal evidence for a group × time interaction ($BF_{inc} = 2.34$, $\eta_p^2 = 0.079$) at 1-month follow-up and moderate evidence against this interaction at 3-month follow-up ($BF_{inc} = 0.31$, $\eta_p^2 = 0.044$). This suggests that the training benefits observed at 1 day post-intervention did not persist over time.

Training data. Performance on the decision-making task across the five training sessions is shown in Fig. 3. Bayesian repeated-measures ANOVAs revealed strong evidence for a main effect of time (session 2: $BF_{10} = 1.66 \times e^8$, $\eta_p^2 = 0.384$; session 3: $BF_{10} = 6.523 \times e^{16}$, $\eta_p^2 = 0.606$; session 4: $BF_{10} = 5.475 \times e^{19}$, $\eta_p^2 = 0.662$; session 5: $BF_{10} = 1.076 \times e^{23}$, $\eta_p^2 = 0.710$) from training session 1, to each of the subsequent training sessions, demonstrating that participants consistently improved their performance over time. There was anecdotal to moderate evidence against a main effect of group, however (session 2: $BF_{10} = 0.405$, $\eta_p^2 = 0.018$; session 3: $BF_{10} = 0.388$, $\eta_p^2 = 0.018$; session 4: $BF_{10} = 0.301$, $\eta_p^2 = 0.015$; session 5: $BF_{10} = 0.329$, $\eta_p^2 = 0.017$), and against a group × time interaction across all of the training sessions (session 2: $BF_{10} = 0.365$, $\eta_p^2 = 0.035$; session 3: $BF_{10} = 0.328$, $\eta_p^2 = 0.033$; session 4: $BF_{10} = 0.476$, $\eta_p^2 = 0.042$; session 5: $BF_{10} = 0.219$, $\eta_p^2 = 0.023$). Thus, there was no evidence for within-session performance benefits or greater training gains for the training + left tDCS group.

Transfer tasks. Far transfer task performance (involved in critical hypothesis tests) is displayed in Fig. 4 (figures for all other tasks and questionnaires are provided in Supplementary Material). As in the trained task, there was moderate to strong evidence against between-group baseline differences on transfer tasks ($BF_{10} < 1/3$; see Extended Data Fig. 1 for individual task statistics). Bayesian repeated-measures ANOVAs revealed strong evidence for a main effect of time ($BF_{inc} > 10$; see Extended Data Fig. 2 for individual task statistics) at 1 day post-intervention and both follow-up time points on visual search, stop-signal, symbol–digit modalities, OSpan and WCST, such that participants' performance improved over time. We also found strong evidence for a main effect of time at both follow-up time points on visual and verbal memory tasks ($BF_{inc} > 10$; see Extended Data Fig. 2 for individual task statistics), again reflecting improvement over time. There was anecdotal to moderate evidence against change in performance over time on the RMET and stimulus detection tasks ($BF_{inc} < 1$; see Extended Data Fig. 2 for individual task statistics). Critically, there was anecdotal to strong evidence against main effects of group or group × time interactions on all transfer tasks and questionnaires, at all post-intervention time points ($BF_{inc} < 1$; see Extended Data Fig. 2 for individual task statistics), suggesting that the training benefits observed on the decision-making task did not transfer to untrained tasks or everyday function at the group level. This is in contrast to the study of Filmer et al.,[21] which found greater improvement on the visual search transfer task following training and left PFC tDCS relative to control groups.

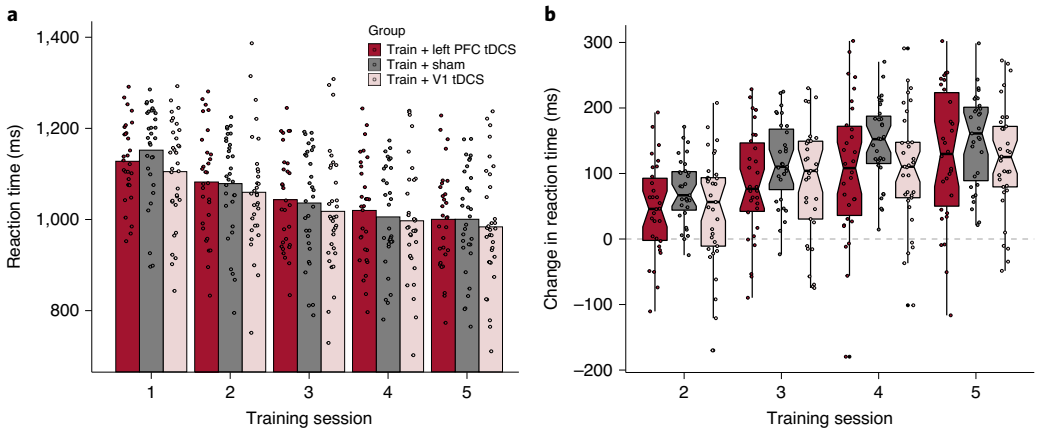

Fig. 3 | Training performance. a, Barplots depicting mean reaction time on the decision-making task for each group in each training session. Individual data points are superimposed on bars. **b**, Notched boxplots with quartile ranges and medians depict reaction time change scores for the decision-making task, in training sessions 2–4 relative to session 1. Individual change scores are superimposed on each boxplot.

Genotype analyses. BDNF Val[66]Met genotype frequencies were as follows: Val/Val = 83, Val/Met = 39, Met/Met = 4. Homozygous Met carriers were excluded from further analyses due to their low frequency. Three samples were inconclusive. *COMT* Val[158]Met genotype frequencies were: Val/Val = 38, Val/Met = 55, Met/Met = 31. Five samples were inconclusive. Both *COMT* and *BDNF* genotypes were in Hardy–Weinberg equilibrium ($\chi^2 = 0.371$; $P = 0.543$).

With respect to *BDNF*, Bayesian pairwise tests found anecdotal to moderate evidence against differences in baseline performance between Val/Val and Val/Met carriers on all of the assessed tasks ($BF_{10} < 1$; see Extended Data Fig. 3 for individual task statistics). Similarly, for *COMT*, one-way Bayesian ANOVAs revealed anecdotal to moderate evidence against between-group differences in baseline performance across all tasks ($BF_{10} < 1$; see Extended Data Fig. 3 for individual task statistics). There was also anecdotal to moderate evidence against a genotype × group x time interaction on the training task and far transfer tasks at each post-intervention timepoint ($BF_{inc} < 1$; see Extended Data Fig. 4 for individual task statistics) for *BDNF* or *COMT*, and only anecdotal evidence for a *COMT* genotype × group × time interaction on the stop-signal task at 3-month follow-up ($BF_{inc} = 1.36$). This suggests that genotypes did not influence participants' response to the intervention on these tasks.

Exploratory analyses. *Individual differences in response to training and tDCS.* Results from the registered analyses suggest that decision-making training and left PFC tDCS did not enhance training benefits, or induce transfer to other tasks at the group level. It is possible, however, that individuals differed in their responses to training and stimulation, and that some participants did indeed benefit from the intervention despite the overall null result. Several studies have found differences in responses to tDCS due to variability in factors such as baseline performance, education and genotype, despite null results at the group level, for example[33–36]. Moreover, the issue of individual differences is particularly relevant in older adults due to differing degrees of structural decline and functional reorganization which can interact with stimulation parameters (for example, intensity)[37]. Indeed, recent studies have shown an influence of age and cortical atrophy on electrical current flow throughout the cortex[38–40]. Rather than conducting a post hoc median split, which would involve false dichotomization of a continuous variable and subsequent loss of power, we employed a linear regression approach to investigate this possibility. Specifically, we conducted Bayesian multiple regressions (using the BayesFactor package in R) on change scores for each far transfer task at 1-month follow-up, in line with registered critical hypothesis tests. Predictors included: (1) an interaction between group and change in decision-making reaction time from pre-intervention to 1 day post-intervention, henceforth referred to as 'training benefit', and (2) baseline scores for the decision-making task and far transfer tasks, as these were expected to co-vary with degree of change on each task. We hypothesized that training benefit would be associated with change in far transfer tasks at 1-month follow-up, for the training + left PFC tDCS group but not for the control groups. In other words, we predicted that individuals who benefitted more from training would show greater improvement on far transfer tasks, only if they received concurrent left PFC tDCS.

To assess the level of evidence for or against each effect, we compared the full model with an equivalent model without the effect of interest. There was anecdotal evidence against a relationship between training benefit and change in visual search ($BF_{10} = 0.73$, $\eta_p^2 = 0.008$) or stop-signal performance ($BF_{10} = 0.43$, $\eta_p^2 = 0.006$) at 1-month follow-up, and for the interaction with group for the stop-signal task ($BF_{10} = 0.43$, $\eta_p^2 = 0.031$). There was anecdotal evidence for an interaction with group for the visual search task (visual search: $BF_{10} = 1.16$, $\eta_p^2 = 0.051$), and anecdotal evidence against a correlation between training benefit and change in OSpan performance ($BF_{10} = 0.45$, $\eta_p^2 = 0.034$). There was moderate evidence for an interaction with group, however ($BF_{10} = 4.42$, $\eta_p^2 = 0.081$), such that training benefit was more associated with improvement on the OSpan task, for the training + left PFC ($\beta = 0.54$, $BF_{10} = 5.89$, $\eta_p^2 = 0.049$) and training + V1 stimulation groups ($\beta = 0.64$, $BF_{10} = 13.06$, $\eta_p^2 = 0.066$) relative to sham. This interaction is depicted in Fig. 5, and demonstrates a positive correlation between training benefit and improvement on the OSpan task for these two active stimulation groups (note that change scores were calculated such that greater scores reflect improvement). There was anecdotal evidence that the control training + left PFC tDCS group differed from sham ($BF_{10} = 1.00$, $\eta_p^2 = 0.012$). The model met the assumptions of linear regression (that is, normally distributed data and residuals, and homoscedascity). In summary, participants who benefitted more from training on the decision-making task and who received active stimulation (regardless of anode site) showed greater improvement on the OSpan task at 1-month follow-up relative to training + sham.

Genotype analyses. In addition to the registered analyses, to maximize the use of our dataset, we investigated whether genotype

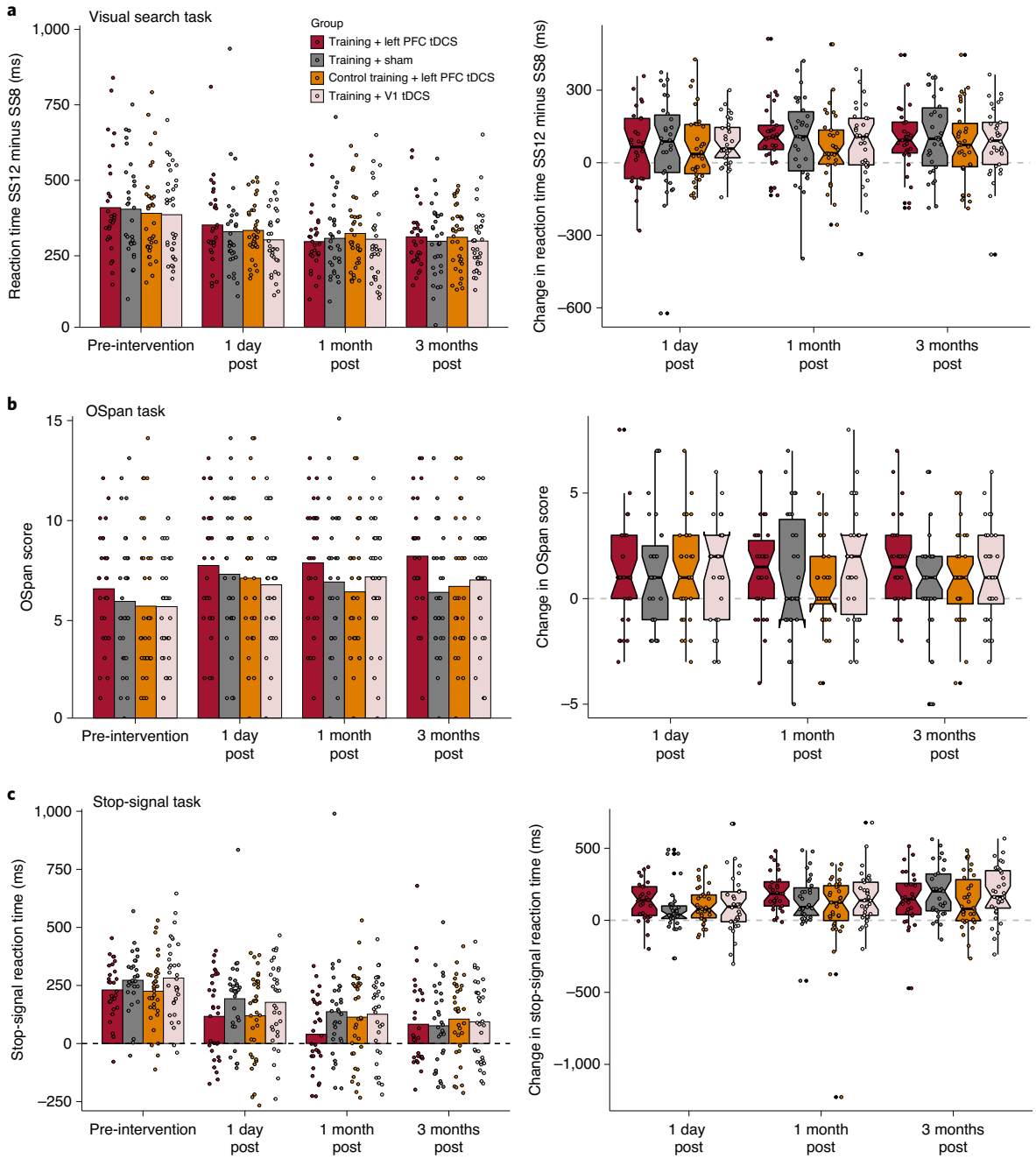

Fig. 4 | Far transfer task performance. a–c, Barplots depicting mean performance for (**a**) visual search task (set size 12 minus set size 8; ms), (**b**) OSpan score and (**c**) stop-signal reaction time (ms) for each group at each time point. Individual data points are superimposed on bars. Notched boxplots with quartile ranges and medians depict change scores relative to baseline for each post-intervention time point. Individual change scores are superimposed on each boxplot.

influenced responses to training and tDCS on any assessed tasks, beyond merely the far transfer tasks. For *COMT* and *BDNF*, we conducted three-way Bayesian ANOVAs on each transfer task at each post-intervention time point to determine whether there was an interaction between genotype, group and time: the same approach used for the registered analyses. We therefore included only training + left PFC tDCS and sham conditions as our groups of interest. Interestingly, for *BDNF* we found moderate evidence for a genotype × group × time interaction on the visual memory task at 3-month follow-up ($BF_{inc} = 6.33$, $\eta_p^2 = 0.124$). Follow-up two-way Bayesian repeated-measures ANOVAs (Fig. 6) for each genotype revealed strong evidence for a group × time interaction for the Val/Val genotype ($BF_{inc} = 16.94$, $\eta_p^2 = 0.247$) such that the training + left PFC tDCS showed greater improvement in recall relative to sham. There was anecdotal evidence against such an interaction for the Val/Met genotype ($BF_{inc} = 0.65$, $\eta_p^2 = 0.055$). There was anecdotal evidence for a *BDNF* × group × time interaction on the WCST at all time points and the verbal memory task at 1 day post- and 3-month follow-up ($BF < 3$; see Extended Data Fig. 4 for individual statistics). There was otherwise anecdotal to moderate evidence against a *BDNF* × group × time or *COMT* × group × time interaction for all other tasks ($BF_{inc} < 1$; see Extended Data Fig. 4 for individual task statistics).

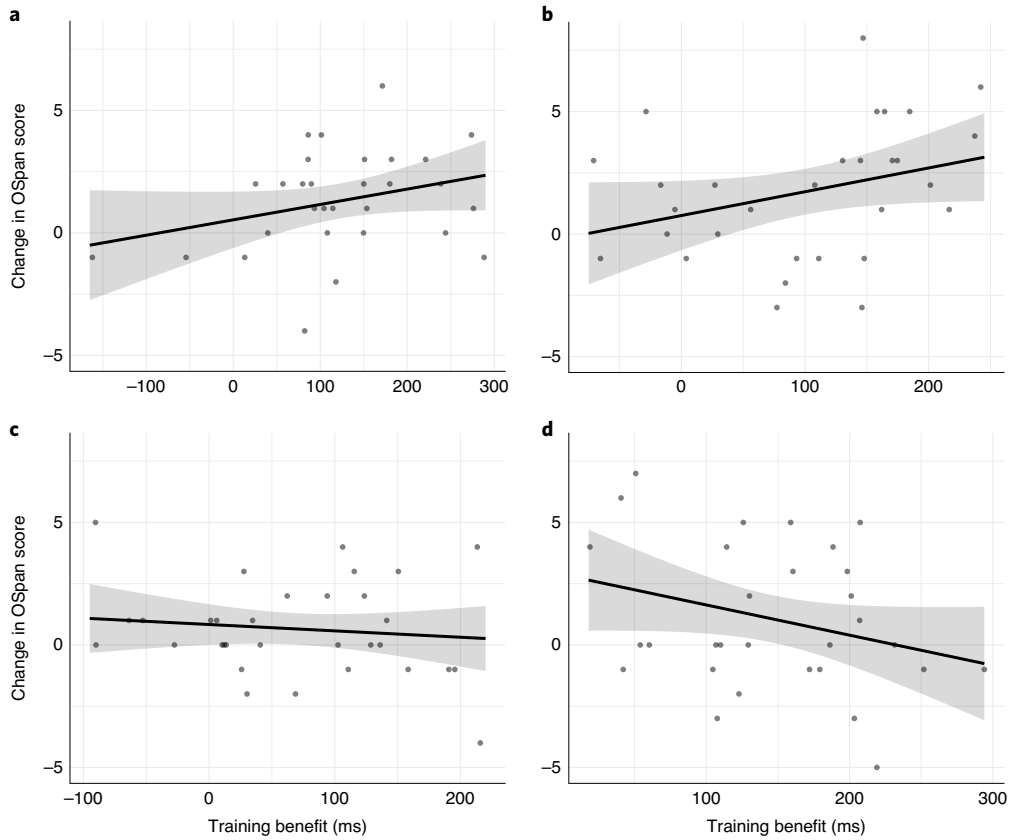

Fig. 5 | Exploratory linear regressions. a–d, Linear regressions depicting the relationship between training benefit and change in OSpan score from pre-intervention to 1-month follow-up. Regressions are plotted separately for each group and labelled as follows: (**a**) training + left PFC tDCS, (**b**) training + V1 tDCS, (**c**) control training + left PFC tDCS and (**d**) training + sham. Participants who benefitted more from training on the decision-making task and active stimulation (regardless of anode site) showed greater benefit on the OSpan task at 1-month follow-up relative to sham.

Discussion

Despite mixed evidence for their efficacy, cognitive training and/or tDCS interventions for age-related cognitive decline have gained popularity within the scientific community and general public. Of particular note is the currently minimal evidence for transfer of training benefits to other cognitive domains or everyday function, and the lack of studies assessing the sustainability of such benefits. The present work aimed to address this issue in a well-powered experimental study employing multiple control groups and comprehensive assessments up to 3-month follow-up. Specifically, we investigated whether repeated sessions of combined decision-making training and left prefrontal tDCS, an approach which has shown strong evidence of transfer in younger adults[21], could induce generalized and sustained cognitive benefits in healthy older adults. Participants attended five sessions of either combined decision-making training + left PFC tDCS, or one of three control protocols, and completed comprehensive cognitive assessments at four time points: immediately before their first session, one day after their final session and at approximately 1 and 3 months post-intervention. The study also adhered to the Registered Report format, and thus underwent peer review before its completion.

As expected, participants who received training on the decision-making task demonstrated greater performance improvement from pre- to 1 day post-intervention compared with those who received training on a control task. However, contrary to our hypotheses and the findings of Filmer at al.[21] in younger adults, there was anecdotal evidence against enhancement of training outcomes on the decision-making task after left PFC tDCS compared with sham or V1 stimulation. There was similarly anecdotal to moderate evidence against between-group differences in performance across training sessions, suggesting that participants who received training + left PFC tDCS improved their decision-making performance at the same rate as individuals allocated to one of the control conditions. This finding also suggests that there were no online, within-session effects of left PFC tDCS.

One possible explanation for these null findings is the change in stimulation parameters across studies, as Filmer et al.[21] employed 0.7 mA stimulation for ~10 min across four sessions, compared with 2 mA for ~20 min across five sessions in the present study. As noted previously, we selected an increased stimulation intensity and duration for use with older adults to increase the likelihood of inducing an effect. Indeed, previous work with older adults has demonstrated dosage effects of PFC tDCS, with stronger stimulation intensities producing greater cognitive benefits[13]. More recently, however, mounting evidence suggests that greater stimulation intensity and duration do not always produce better outcomes[41]. For example, with older adults, one study found no effect of 20 sessions of 2 mA stimulation on behaviour[26]; conversely, another study found gains in attentional control following only three sessions of 1.5 mA tDCS[42]. Hence, along with the possibility that there are no effects of decision-making training and tDCS on older adults in general, it may be the case that we failed to replicate Filmer et al.'s[21] findings due to the increase in the number of sessions and stimulation intensity. In addition, electrophysiological studies have demonstrated that 2 mA stimulation increases the excitability of motor evoked potentials under the anode and cathode electrodes, whereas lower intensities have been shown to increase and decrease excitability under the anode and cathode, respectively[43,44]. It is therefore

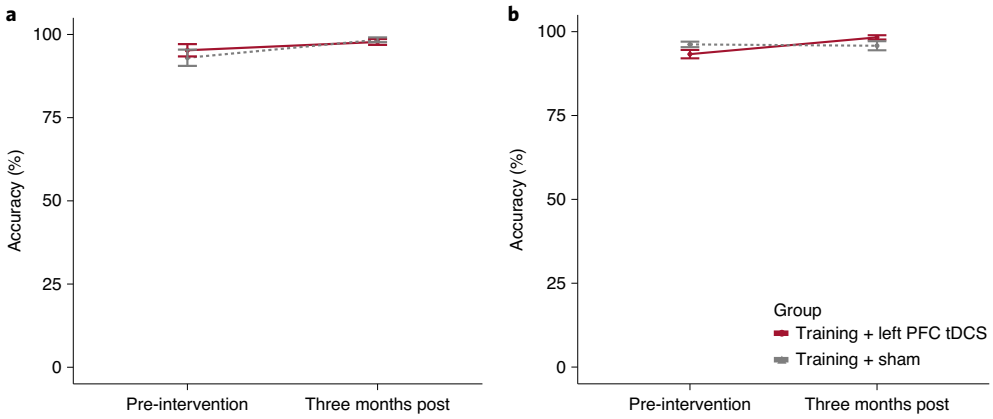

Fig. 6 | Exploratory genotype analyses. a,**b**, Mean accuracy on the visual memory task at pre-intervention and 3-month follow-up for Val/Met (**a**) and Val/Val (**b**) genotypes. Error bars denote standard errors.

possible that the montage employed by the current study elicited a different pattern of cortical excitation/inhibition than that induced by Filmer et al.[21], producing different behavioural outcomes.

Anecdotal evidence against a stimulation effect might also be attributable to marked changes in cerebral structure and function associated with ageing, meaning that findings in younger participants do not necessarily translate to older adult populations[11,37]. Indeed, previous work has even found opposing effects of the same stimulation parameters in young and older adults[45,46], while effects found only during left PFC tDCS in younger adults have been found irrespective of stimulation site in older adults[47]. Such differences might reflect structural brain changes such as reductions in volume and cortical thickness, as well as alterations in excitability and functional lateralization[11]. For example, increases in distance between the cortex and scalp and cerebrospinal fluid (CSF) volume can alter the flow of electrical current and its impact on neuronal tissue[48]. This was suggested in a recent computational modelling study, which found that older adults required higher intensities of stimulation than their younger counterparts to achieve the same current density within the dorsolateral prefrontal cortex (DLPFC), in part due to changes in brain-to-CSF ratio[38]. This suggests that the 2 mA intensity employed in the current study may not have been sufficient to induce substantial changes in performance. The same study also found the greatest electrical field values between rather than directly underneath the anode and cathode, suggesting that future studies should carefully consider electrode placement in older adult participants rather than relying on findings in younger adults. These mechanisms would likely differ again in clinical populations such as those with mild cognitive impairment and dementia, but this is yet to be investigated. In summary, there are several plausible reasons for the findings against a tDCS-induced training benefit in the current study. However, it is also possible that tDCS simply does not enhance decision-making training benefits in older adults regardless of stimulation duration or intensity.

Our critical hypothesis predicted that participants who received combined training and left PFC tDCS would display performance benefits on far transfer tasks at 1-month follow-up, a result we believed would have meaningful implications for the field. Contrary to this prediction, we found evidence for the null hypothesis on the three far transfer tasks (visual search, stop-signal task and OSpan), demonstrating that training and stimulation did not enhance performance. Indeed, strong evidence in favour of the null hypothesis was achieved for each of these tasks through a Bayesian sampling approach. Despite this, the Bayes factor for the group × time interaction on the stop-signal task (initially >10) reduced markedly when data collection was completed, and at this point indicated only anecdotal evidence for the null hypothesis. It is less clear whether training benefits might have transferred to this task, but anecdotal evidence in favour of the null in our large sample size is nonetheless an important finding. We note that some participants adopted a strategy that prioritized accuracy over reaction times, and often waited for the stop-signal tone before responding, despite being instructed not to wait for the stop signal. This strategy at times resulted in negative SSRT values. To ensure these did not substantially influence the results, we re-analysed the data excluding negative values and found minimal changes in the pattern of findings or Bayes factors. There was similarly anecdotal to strong evidence for no benefit of training and left PFC tDCS on any other transfer tasks or questionnaires across the post-intervention time points. Thus, hypothesis 2, which predicted performance benefits for the training and stimulation groups on all executive function tasks and questionnaires at all post-intervention time points, was not supported. This finding could be attributed to the apparent lack of tDCS-induced training benefit, although some studies have shown tDCS-induced transfer to unrelated tasks despite no benefit on trained tasks[13]. Regardless of the reason, it seems that decision-making training and tDCS are unlikely to produce meaningful transfer gains or improved everyday function (for example, participation in ADLs) in healthy older adults, at least with the current protocol.

As there are often individual differences in participants' responses to training and/or stimulation interventions, which can influence findings at the group level, we investigated this possibility further in exploratory analyses which cannot contribute to the study conclusions but are nonetheless interesting. These analyses revealed moderate evidence that greater training benefits on the decision-making task were associated with greater performance improvement at 1-month follow-up, only for participants who received active stimulation (regardless of site) paired with decision-making training, partially supporting our post hoc hypothesis. Interestingly, as V1 was used as a control electrode location, we did not predict any transfer benefits for this group, but this could be attributed to a common effect of the right orbitofrontal cathode in both active conditions.

In addition to group-level analyses, we investigated whether responses to training + tDCS differed depending on Val/Met polymorphisms of *COMT* and *BDNF* genes. Despite previous evidence for an effect of genotype on cognitive functions in older adults[49], we found anecdotal to moderate evidence against differences in baseline performance across *BDNF* and *COMT* genotypes. There was also anecdotal to moderate evidence against an effect of *COMT* or *BDNF* genotype on response to intervention on our key far transfer

tasks at 1-month follow-up. To maximize the use of our data, we conducted further exploratory analyses on all other transfer tasks (following the registered analysis steps) at all post-intervention time points, which again cannot contribute substantively to conclusions due to their post hoc nature. For most of the tasks we found anecdotal to moderate evidence against an effect, or anecdotal evidence for an effect of *COMT* or *BDNF* genotype on response to intervention. However, there was moderate evidence that *BDNF* Val/Val carriers who received training + left PFC tDCS showed improved visual memory performance at 3-month follow-up, relative to sham. This result suggests that, for Val/Val carriers, decision-making training + left PFC tDCS induced long-term improvement in an unrelated cognitive domain (visual episodic memory), but this requires replication in confirmatory research before any conclusions can be drawn.

Methods

The study was approved by the UQ Human Research Ethics Committee (approval no. 2017000958). All participants provided informed, written consent.

Overview. We assigned 133 older adult participants to one of four matched groups, as described in detail below. Each group received one of the following stimulation protocols over five sessions, on consecutive days: training + tDCS over the left PFC, training + sham tDCS (over the left PFC), control training + tDCS over the left PFC or training + tDCS over V1 (a control electrode location). We assessed participants on a battery of tasks and questionnaires, immediately before their first stimulation session, 1 day after their final stimulation session and at approximately 1- and 3-month follow-up. Assessment tasks assessed a broad range of executive functions including decision-making, working memory, multitasking, inhibition, cognitive flexibility and theory of mind, as well as verbal and visual episodic memory. Ecologically valid questionnaires, completed by the participant and a nominated significant other (for example, partner or family member where available), assessed participants' executive functions in everyday life, and their completion of instrumental ADLs (IADLs). We were unable to obtain informant data for eight participants due to informants not responding to correspondence or participants not nominating a suitable candidate. Finally, two control tasks (symbol–digit modalities test and stimulus detection task) were used to ensure that any improvement on executive function tasks was not due to general changes in motor speed and/or speed of processing. Most assessment tasks employed pseudo-randomized stimuli and trial orders, which were different at each testing time point, thus minimizing any practice effects. The memory tasks employed parallel versions. For other tasks, such as the RMET and the WCST computerized version, where parallel versions are not available, practice effects may have occurred. This is not considered problematic, however, as all groups are susceptible to the same practice effects. We note that the increased social contact arising from participation in this study might itself have an effect on cognitive functioning in older adults. Critically, however, social contact was held constant across stimulation groups, and therefore should not have affected our key hypotheses.

It has been suggested that individual differences in genetic factors are associated with an individual's response to tDCS, in particular, catechol-*O*-methyltransferase (*COMT*) and brain-derived neurotrophic factor (*BDNF*) genotype profiles. For example, Plewnia et al.[50] found that, for the *COMT* gene, homozygous Met carriers displayed poorer cognitive flexibility following prefrontal anodal tDCS, whereas homozygous Val or heterozygous carriers showed no such effect. In addition, greater motor evoked potential facilitation was shown following tDCS in homozygous Met carriers for the *BDNF* gene, than homozygous Val or heterozygous carriers, as well as an enhanced neurophysiological response[51]. Although it was not the primary goal of the current study to investigate individual differences, genotyping may assist in determining which individuals will respond best to tDCS and training. Thus, here we also examined the influence of *COMT* and *BDNF* polymorphisms on baseline performance, and response to intervention on the decision-making and far transfer tasks. This involved collecting a 0.75 ml saliva sample for genotyping from each participant during the first session.

Participants. *Recruitment and inclusion criteria.* We recruited 133 participants aged 60–75 years via advertisements across multiple media, including television, radio and local newspapers. Finally, 129 participants (75 female, mean age = 67.62 ± 4.21 years, mean education = 15.47 ± 3.35 years, 12 participants left handed on the Edinburgh Handedness Inventory[52]) were included in analyses as 2 participants missed one or more stimulation sessions and 2 participants withdrew from the experiment. In addition, recruitment involved The University of Queensland (UQ) '50 Plus Registry', staff newsletters and social media, as well as flyers at local community organizations (for example, bowls clubs and retirement villages) and the UQ St Lucia Campus. We emphasized community, rather than university, recruitment in an attempt to achieve a more representative sample of the general population of older adults. To be included, participants were required to have normal or corrected to normal vision and hearing, and to meet the following criteria: (1) no evidence of mild cognitive impairment or dementia (Montreal Cognitive Assessment (MoCA) ≥26; mean score 28.26 ± 1.30), (2) no current use of psychiatric medication(s), (3) no psychiatric or neurological condition(s) (for example, previous stroke or epilepsy), (4) no contraindications to brain stimulation as determined by a tDCS safety screening questionnaire (for example, metal in the head, implanted neurostimulator or skin conditions of the scalp) and (5) no clinically significant depressive symptoms (Beck Depression Inventory >13). They also completed measures of physical activity/exercise (Yale Physical Activity Scale[53]), which were used for group allocation (below).

Following recruitment and screening, we allocated participants to demographically matched groups based on age, gender, education and physical activity, using a stratified sampling approach, with approximately equal participant numbers per group. There was no evidence for between-group differences in age, gender, education, physical activity or MoCA score ($BF_{10} < 1/3$). We allocated couples attending sessions together to the same training task (decision-making or 'control' training) to ensure they remained blinded to their allocated group if discussing their participation. Before commencing the stimulation phase of the study, participants were required to achieve ≥70% accuracy on the training task during the initial assessment session. A score ≥70% indicated that participants had understood task instructions and learned response mappings correctly. As the participants had greater difficulty learning this task than anticipated, those who struggled were allowed additional practice blocks to achieve this threshold. To be included in the final analyses, participants must have attended all training sessions, pre- and immediate post-intervention assessment sessions, and have complied with instructions throughout the experiment.

Bayesian sampling plan. In adherence to the Bayesian sampling approach, we did not predetermine a sample size for this study. Instead, we recruited participants until a $BF_{10} > 10$ or $BF_{01} > 10$ was established for the critical hypothesis tests, providing strong evidence for the alternative or null hypothesis, respectively. This approach afforded more informative results than those achieved through frequentist methods[30].

Behavioural assessment. Participants were assessed on a computerized battery of tasks at pre- and post-intervention and 1- and 3-month follow-up. This included the decision-making trained task, six additional executive function tasks, verbal and visual episodic memory tasks and two processing/motor speed control tasks. Behavioural tasks were selected to encompass a broad range of executive functions, with differing degrees of overlap with the trained task. We also selected two episodic memory tasks, to determine the utility of the training and stimulation protocol for enhancing long-term memory, and whether transfer extends beyond executive functions. All experimental tasks were based on versions of paradigms that have previously been used in older adult populations (examples provided below).

Executive function tasks assessed the following key areas: working memory, multitasking/task-switching, inhibition, cognitive flexibility and theory of mind, and were categorized as 'near' and 'far' transfer, or 'translational' tasks, within this domain. Categorizations were based on similarity to the trained task across properties such as type of stimuli, stimulus modality (for example, visual versus auditory) and response type (for example, response selection versus inhibition of a response). It should be acknowledged that the categorization of transfer tasks remains debated within the literature[54], but for the purposes of the current project, and for distinguishing between different types of executive functions that are inherently related, we believe the current principles of task categorization are appropriate. Episodic memory tasks, however, assessed verbal and visual recognition memory and reflected transfer to a different cognitive domain, with evidence to suggest a distinction between episodic memory and executive functions[55]. We describe all tasks briefly here, and in greater detail, including scoring procedures, in the Supplementary Material. Unless otherwise stated, participants were instructed to complete tasks as quickly and accurately as possible.

Training task. The training task required speeded discrimination between several auditory stimuli, as a measure of decision-making[21]. Participants were presented with one of six different complex tones, and responded to each with a corresponding keypress. Training on this task aimed to increase the speed at which participants could execute a decision. A similar auditory discrimination task was used by Bherer et al.[56], in an older adult population.

Control training task. In the control training task, participants were presented with a rapid serial visual presentation (RSVP) stream of distractor numbers, and reported the identity of a single target letter, via a keypress response at the end of the stream[57–59]. The presentation speed of all stimuli was adjusted for each participant such that accuracy was held at approximately 75%. Thus, the dependent variable for this task was the exposure duration of the stream, with shorter exposure durations indicating better performance. Critically, as noted, performance on this task is assessed via accuracy, rather than reaction time, so as to keep it engaging and challenging for participants, while differentiating it

from the decision-making training task. This task is a simplified version of the extensively used attentional blink paradigm, which was used by Lahar et al.[60] in an older adult population.

Near transfer task. A single near transfer task assessed decision-making and its capacity limits for auditory and visual stimuli, in a multitasking paradigm, thus involving the same type of stimuli and response as the training task, with additional visual stimuli and a task-switching component. We used the 'single versus dual-task' from Bender et al.[61], which involved single and concurrent presentation of auditory and visual decision-making tasks. In each task, participants discriminated between two different stimuli (auditory or visual) with a keypress response. Performance was indexed as a reaction time cost between single and dual tasks. A similar dual-task paradigm was used by Bherer et al.[56] with older adults.

Far transfer tasks. We included three far transfer, executive function tasks, to assess the domains of visuospatial attention, working memory and response inhibition, which are considered related but distinguishable cognitive processes to decision-making. First, we included the visual search task used in Filmer et al.[21], in which participants were required to find a target letter ('T') in arrays of multiple, rotated, distractor letters ('L'), and indicate whether the target was rotated 90° to the left or right, via a keypress response. As noted previously, this task involves a different stimulus modality from the training task and requires a different response (finding a stimulus amongst distractors versus selecting the correct response to a presented stimulus), and is thus considered a far transfer measure. Second, we included an automated version of the OSpan task[61], in which participants were presented with a sequence of letters, with intermittent simple math equations. Participants were required to solve each math equation as it was presented, and to remember the letters over multiple trials to be recalled at the end of a block. This task not only includes visual rather than auditory stimuli, but also involves retaining information in the face of distraction, responding with a mouse- rather than a keypress, and has a focus on accuracy rather than speed, warranting its inclusion as a far transfer task. Finally, we administered the stop-signal task used in Bender et al.[61], in which participants must discriminate between two different abstract shapes on 'go' trials (75% of trials), but withhold their response on "stop signal" trials (25% of trials). Stop-signal trials are indicated by a brief auditory tone after the shape presentation, at varying intervals. Categorized as far transfer, this task involves both auditory and visual stimuli, and assesses the ability to withhold a pre-potent response rather than being able to select and execute a speeded decision. All far transfer tasks have previously been used in older adult populations[13,62–64].

Translational tasks. Two translational tasks were administered, assessing cognitive flexibility and theory of mind. Both tasks differed from the training task in that they involved visual (versus auditory) stimuli, were accuracy (versus speed) based, required mouse (versus keyboard) responses and critically, involved complex abstract reasoning processes (versus decisions based on simple stimulus properties). The first translational task was a computerized version of the WCST[65], in which participants sorted cards according to changing categorical principles (by colour, shape or number). They were presented with four piles of cards, and sorted a stimulus card according to a changing sorting rule (for example, sort by colour). However, participants were not told the sorting rule, and were instead required to use corrective feedback to determine whether their response was correct, and hence deduce what the current rule was. Second, we administered a computerized version of the RMET[66]. Participants identified a person's mental state based on an image of their eyes, from four options, with a keypress response. Both translational tasks have previously been used in older adult populations by Gunning-Dixon and Raz[67] and Luck et al.[68], respectively.

Memory tasks. We included two episodic memory tasks to assess recognition memory for verbal and visual information. Participants viewed a series of words or pictures of objects, for the verbal and visual tasks, respectively. They were then shown pairs of stimuli (either words or pictures), after a 10-min delay. Their task was to report, with a keypress response, which of the two stimuli in each pair they were shown previously, with one of the items being a foil. Similar verbal and visual tasks have been used previously to assess episodic memory in older adults[47,69,70]. Critically, we included visual and verbal tasks because prefrontal activity is thought to interact with the type of material to be remembered, with more left-sided or bilateral involvement for verbal material[70–73] and more right-sided involvement for visuospatial material[74]. Therefore, it is possible that the current protocol might influence performance for one type of stimulus material, but not the other. We also note that participants may have used verbalizing strategies to remember visual material. To address this, each pair of pictures included two images of the same object—one that was seen previously, and one that was not (objects were selected from the database employed by Brady et al.[75]). For example, if one of the objects was a chair, participants chose between the to-be-remembered chair and a distractor chair.

Control tasks. We included two control tasks that assessed speed of processing and motor responses (as in Anguera et al.[76], with older adults). The first was a computerized Symbol Digit Modalities Task[77], in which participants were given nine symbol–digit pairs, followed by a list of 120 symbols. Participants inserted the corresponding digit under each symbol as quickly as possible, with a keypress response. They were given 120 s to complete as many symbol–digit pairs as possible. The second control task was a basic stimulus detection task, whereby participants fixated centrally, and made a speeded keypress response when a target stimulus appeared (grey circle on a white background).

Self- and informant-report questionnaires. Participants and their nominated significant other completed self-report and informant versions of the BRIEF-A[78] assessing participants' use of executive function behaviours in everyday life, and the FAI[79], a brief measure of IADLs, designed for use in stroke patients, but more recently validated in healthy adults[80]. The BRIEF-A included 75 statements such as: 'Has trouble changing from one activity or task to another' and 'Makes careless errors when completing tasks'. Participants and informants responded by answering the question: 'During the past 6 months, how often has each of the following behaviors been a problem?', with 'Never' (1), 'Sometimes' (2) or 'Often' (3). Scores were standardized as T scores according to the BRIEF-A manual, with higher scores indicating poorer executive function. The FAI included 15 items such as 'Preparing main meals', 'Light housework', 'Social occasions' and 'Driving car/going on bus', which can be broken into subscales: domestic chores, leisure/work and outdoor activities. Participants/informants rated the participant on a four-point scale (0–3) based on the frequency with which activities were completed. Participants were given a score for each subscale, and an overall FAI score, with higher scores indicating better completion of IADLs.

Genotyping. We collected a saliva sample from each participant in the first assessment session, for *COMT* Val^{158}Met (rs4680) and *BDNF* Val^{66}Met (rs6265) genotyping. Genotyping was completed off-site (Monash University, Australia). The *COMT* rs4680 polymorphism was genotyped as described in Hawi et al.[81], and *BDNF* rs6265 was genotyped using an Applied Biosystems TaqMan assay running on a Roche LightCycler 480, following the manufacturer's instructions.

Training/stimulation protocols. Each group of participants received one of four intervention protocols: (1) combined training and concurrent anodal tDCS over the left PFC, (2) combined training and concurrent sham tDCS over the left PFC, (3) combined training and concurrent anodal tDCS over V1 and (4) combined control training and concurrent anodal tDCS over the left PFC. Participants received five sessions of their stimulation protocol across consecutive days, at approximately the same time each day. Critically, we added a session, and doubled the duration of training and stimulation relative to Filmer et al.[21], who observed reliable and long-lasting (2 week) transfer, to increase the likelihood of observing effects on cognition.

A double blind procedure for the key conditions was implemented. To wit, participants were blinded to their experimental condition, and for conditions involving combined decision-making training and left PFC electrode placement, the experimenter was also blinded to the type of stimulation participants received (active or sham). Experimenter blinding was not possible for the other conditions, as the V1 electrode location and the control training task revealed the current condition. After every session, participants completed a questionnaire assessing for the presence of any adverse effects.

tDCS montage. tDCS was administered with a NeuroConn DC stimulator, using 5 × 5 cm electrodes. 'Study mode' was used for double blinding, such that experimenters entered a code corresponding to active or sham stimulation. For left PFC stimulation, the target electrode was placed 1 cm posterior to F3 (the posterior part of Brodmann area 9) using the 10–20 electroencephalography system[82], and the reference electrode was placed on the right supraorbital region. We chose this configuration based on Filmer et al.[21], where combined decision-making training and stimulation produced transfer benefits on a visual search task. The left PFC was targeted on the basis of its established relationship with decision-making processes[83–85] and executive functions more broadly. Indeed, this region has often been targeted in brain stimulation studies that have aimed to enhance executive functions, such as working memory and attention[13,33,86], and the orbitofrontal cortex has frequently been used as a cathode location in studies targeting the PFC[21,26,85,87]. Critically, this cathode location was also used in the V1 stimulation condition, thus controlling for any effect of this electrode location on performance. Specifically, for V1 stimulation, the target electrode was placed over Oz, with the reference electrode placed over the right supraorbital region[88].

All stimulation conditions employed a current intensity of 2.0 mA (current density 0.08 mA cm^{-2}). This stimulation strength was chosen because recent studies have reported promising effects of 2 mA anodal tDCS in older adults[13,45,86], with one study showing dosage-related effects of tDCS over the PFC, with stronger intensities producing greater benefits[13]. Anodal stimulation remained constant for 19 min, with an additional 30 s of ramp up and ramp down time (20 min total). The sham condition followed the same timings except that active stimulation remained on for only 30 s before ramping down. Participants completed the training or control-training task for the 20 min of stimulation (anodal or sham). To further ensure experimenter and participant blinding, impedance values were presented

on-screen throughout the stimulation period, in both active and sham conditions. Due to an oversight, we did not ask participants or the experimenter to guess the stimulation condition. For the most part, however, adverse effects questionnaires indicated no differences in the experience of stimulation (tingling: $BF_{10}=0.08$, $\eta^2=0.014$; scalp soreness: $BF_{10}=0.16$, $\eta^2=0.00$; neck soreness $BF_{10}=0.45$, $\eta^2=0.048$; burning $BF_{10}=0.11$, $\eta^2=0.020$, headache: $BF_{10}=0.25$, $\eta^2=0.036$; concentration: $BF_{10}=0.33$, $\eta^2=0.042$; mood: $BF_{10}=0.14$, $\eta^2=0.00$) between the training + left PFC tDCS group and control groups. There was a difference in itching ($BF_{10}=4.26$, $\eta^2=0.089$), such that the V1 tDCS condition experienced more itching than the sham condition ($BF_{10}=8.21$, $d=0.729$), likely due to the V1 electrode often being placed over hair and thus increasing impedance. This is not of particular concern, as the V1 stimulation condition was also a control. Importantly, there was no difference between both active left PFC tDCS groups and sham ($BF_{10}=0.59$, $d=0.357$; $BF_{10}=0.59$ $d=0.351$). There was also a difference in skin redness between both left PFC tDCS groups relative to sham ($BF_{10}=6.51$, $\eta^2=0.097$), which is unlikely to have affected participant blinding, as participants could not see the redness on their scalp, but possibly weakened experimenter blinding.

Protocol registration. The stage 1 protocol for this Registered Report was accepted in principle on 9 December 2017. The protocol, as accepted by the journal, can be found at https://osf.io/xhym8/.

The sentence 'This study is the first within the field to adhere to the Registered Report format.' was removed from the 'Introduction' before acceptance of the stage 2 manuscript on editorial request, in order to comply with journal policies regarding priority claims.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

All data files are available at: https://osf.io/e2u73.

Code availability

Analysis code is provided at: https://osf.io/e2u73.

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Author contributions

K.S.H. was involved in all aspects of the study, including study design, project planning, recruitment and data collection, data analysis and manuscript preparation. H.L.F. also contributed to each of these aspects. Z.E.N. contributed to project planning and data collection. Z.H. and K.P. were responsible for extraction and analysis of genetic data. J.B.M. contributed to study design and manuscript preparation. P.E.D. was involved in study design, project planning, data analysis and manuscript preparation.

Competing interests

The authors declare no competing interests.

Additional information

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Task	BF_{10}	η^2
Decision-making task	0.259	0.034
Visual search task	0.061	0.004
Single vs dual task	0.085	0.013
Stop-signal task	0.246	0.032
RMET	0.086	0.014
WCST	0.102	0.029
Verbal memory	0.063	0.014
Visual memory	0.075	0.011
SDMT	0.076	0.016
Stimulus detection task	0.227	0.029
BRIEF-A Self report	0.058	0.007
BRIEF-A Informant report	0.054	0.004
FAI Self report	0.101	0.019
FAI Informant report	0.056	0.003

Extended Data Fig. 1 | Individual task and questionnaire statistics for one way ANOVA on baseline performance. Note: BF >10 indicates strong support for H_1 over H_0; BF >3 indicates moderate support for H_1 over H_0; 1< BF <3 indicates anecdotal support for H_1 over H_0; 1/3< BF <1 indicates anecdotal support for H_0 over H_1; 1/10< BF <1/3 indicates moderate support for H_0 over H_1; BF <1/10 indicates strong evidence for H_0 over H_1; BF = 1 indicates no evidence for H_0 or H_1.

Task	Time 1 vs. Time 2			Time 1 vs. Time 3			Time 1 vs. Time 4		
	Time BF_{inc} / η_p^2	Group BF_{inc} / η_p^2	Group x time BF_{inc} / η_p^2	Time BF_{inc} / η_p^2	Group BF_{inc} / η_p^2	Group x time BF_{inc} / η_p^2	Time BF_{inc} / η_p^2	Group BF_{inc} / η_p^2	Group x time BF_{inc} / η_p^2
Decision-making task	3.097e + 22 / 0.615	0.205 / 0.018	22.149 / 0.116	4.444e +16 / 0.507	0.217 / 0.018	2.442 / 0.079	1.466e + 15 / 0.468	0.207 / 0.016	0.367 / 0.044
Single-vs-dual-task	0.362 / 0.015	0.111 / 0.021	0.115 / 0.020	2.004 / 0.042	0.105 / 0.019	0.043 / 0.001	0.349 / 0.015	0.074 / 0.016	0.077 / 0.012
Visual-search task	17485.134 / 0.178	0.095 / 0.013	0.051 / 0.013	4.195e +6 / 0.256	0.055 / 0.001	0.086 / 0.014	8.444e +7 / 0.286	0.058 / 0.003	0.074 / 0.006
O-Span task	470749.073 / 0.217	0.201 / 0.014	0.048 / 0.003	13342.457 / 0.176	0.257 / 0.021	0.088 / 0.015	44466.944/ 0.197	0.377 / 0.029	0.301 / 0.041
Stop-signal task	4.196e +8 / 0.308	0.662 / 0.051	0.078 / 0.012	1.471e +9 / 0.331	0.235 / 0.035	0.409 / 0.046	1.424e +15 / 0.443	0.066 / 0.009	0.134 / 0.023
RMET	0.271 / 0.010	0.225 / 0.023	0.161 / 0.028	0.567 / 0.026	0.091 / 0.012	0.076 / 0.012	0.518 / 0.025	0.106 / 0.008	0.115 / 0.022
WCST	1.745e +10 / 0.345	0.273 / 0.029	0.050 / 0.003	5.223e +14 / 0.453	0.264 / 0.024	0.115 / 0.020	7.971e +13 / 0.437	0.125 / 0.013	0.239 / 0.036
Verbal memory task	0.408 / 0.019	0.172 / 0.018	0.059 / 0.008	108398.239 / 0.213	0.137 / 0.010	0.167 / 0.030	55.716 / 0.104	0.090 / 0.003	0.346 / 0.043
Visual memory task	2.637 / 0.048	0.075 / 0.013	0.121 / 0.022	1.160e +8 / 0.286	0.111 / 0.020	0.052 / 0.004	182669.961 / 0.205	0.058 / 0.009	0.119 / 0.022
Stimulus detection task	0.249 / 0.010	0.241 / 0.018	0.101 / 0.020	0.294 / 0.014	0.291 / 0.025	0.074 / 0.012	0.242 / 0.010	0.328 / 0.031	0.045 / 0.000
Symbol-digit modalities	1.270e +18 / 0.514	0.318 / 0.021	0.090 / 0.016	1.602e +14 / 0.443	0.216 / 0.017	0.256 / 0.036	5.281e +15 / 0.481	0.227 / 0.019	0.314 / 0.043
BRIEF-A Self report	268.501 / 0.127	0.253 / 0.007	0.070 / 0.007	153.190 / 0.126	0.283 / 0.005	0.798 / 0.066	1103.574 / 0.155	0.160 / 0.005	0.231 / 0.044
BRIEF-A Informant report	6.730 / 0.069	0.274 / 0.003	0.231 / 0.037	12.580 / 0.083	0.281 / 0.003	0.059 / 0.006	18.781 / 0.090	0.350 / 0.011	0.112 / 0.023
FAI Self report	0.244 / 0.010	0.442 / 0.021	0.080 / 0.015	0.151 / 0.002	0.427 / 0.026	0.188 / 0.028	0.165 / 0.003	0.249 / 0.025	0.065 / 0.009
FAI Informant report	0.188 / 0.003	0.298 / 0.006	0.105 / 0.019	0.198 / 0.006	0.261 / 0.008	0.073 / 0.007	0.344 / 0.016	0.255 / 0.003	0.085 / 0.009

Extended Data Fig. 2 | Individual task and questionnaire statistics for the group x time interaction for all time points. Note: BF >10 indicates strong support for H_1 over H_0; BF >3 indicates moderate support for H_1 over H_0; 1< BF <3 indicates anecdotal support for H_1 over H_0; 1/3< BF <1 indicates anecdotal support for H_0 over H_1; 1/10< BF <1/3 indicates moderate support for H_0 over H_1; BF <1/10 indicates strong evidence for H_0 over H_1; BF = 1 indicates no evidence for H_0 or H_1.

Task	COMT		BDNF	
	BF_{10}	η_p^2	BF_{10}	*d*
Decision-making task	0.568	0.037	0.300	0.179
Single-vs-dual-task	0.191	0.018	0.375	-0.226
Visual-search task	0.235	0.021	0.335	0.203
O-Span task	0.174	0.016	0.517	-0.280
Stop-signal task	0.111	0.006	0.688	0.323
RMET	0.116	0.007	0.280	-0.161
WCST	0.178	0.016	0.449	-0.258
Verbal memory task	0.107	0.005	0.440	-0.257
Visual memory task	0.173	0.015	0.759	-0.332
Stimulus detection task	0.187	0.017	0.367	0.222
Symbol-digit modalities	0.197	0.018	0.550	-0.289

Extended Data Fig. 3 | Individual task statistics for the effect of genotype on baseline performance. Note: COMT statistics are derived from one-way ANOVAs and BDNF statistics are derived from independent samples t-tests due to the exclusion of Met/Met alleles from analyses. BF >10 indicates strong support for H_1 over H_0; BF >3 indicates moderate support for H_1 over H_0; 1< BF <3 indicates anecdotal support for H_1 over H_0; 1/3< BF <1 indicates anecdotal support for H_0 over H_1; 1/10< BF <1/3 indicates moderate support for H_0 over H_1; BF <1/10 indicates strong evidence for H_0 over H_1; BF = 1 indicates no evidence for H_0 or H_1.

Task	COMT						BDNF					
	Time 1 vs. Time 2		Time 1 vs. Time 3		Time 1 vs. Time 4		Time 1 vs. Time 2		Time 1 vs. Time 3		Time 1 vs. Time 4	
	BF_{inc}	η_p^2	BF_{inc}	η_p^2	BF_{inc}	η_p^2	BF_{inc}	η_p^2	BF_{inc}	η_p^2	BF_{inc}	η_p^2
Decision-making task	0.311	0.001	0.392	0.026	0.260	0.006	0.392	0.001	0.461	0.008	0.329	0.000
Single-vs-dual-task	0.243	0.008	0.247	0.001	0.270	0.008	0.319	0.001	0.372	0.012	0.539	0.019
Visual-search task	0.396	0.029	0.606	0.049	0.371	0.059	0.368	0.006	0.791	0.033	0.414	0.008
O-Span task	0.320	0.023	0.282	0.005	0.299	0.014	0.367	0.002	0.808	0.040	0.539	0.020
Stop-signal task	0.727	0.068	0.221	0.003	1.355	0.100	0.393	0.007	0.394	0.004	0.556	0.016
RMET	0.349	0.034	0.503	0.047	0.227	0.008	0.331	0.000	0.468	0.006	0.524	0.020
WCST	0.380	0.035	0.329	0.027	0.457	0.044	1.615	0.068	2.751	0.101	1.360	0.073
Verbal memory task	0.222	0.012	0.638	0.048	0.513	0.038	1.060	0.042	0.489	0.008	1.335	0.056
Visual memory task	0.321	0.015	0.255	0.007	0.301	0.012	0.813	0.034	0.534	0.014	6.333	0.109
Stimulus detection task	0.425	0.036	0.512	0.031	0.416	0.037	0.317	0.000	0.776	0.038	0.472	0.012
Symbol-digit modalities	0.738	0.059	0.547	0.047	0.578	0.053	0.661	0.025	0.377	0.007	0.472	0.012

Extended Data Fig. 4 | Individual task statistics for the genotype x group x time interaction. Note: COMT statistics are derived from one-way ANOVAs and BDNF statistics are derived from independent samples t-tests due to the exclusion of Met/Met alleles from analyses. BF >10 indicates strong support for H_1 over H_0; BF >3 indicates moderate support for H_1 over H_0; 1< BF <3 indicates anecdotal support for H_1 over H_0; 1/3< BF <1 indicates anecdotal support for H_0 over H_1; 1/10< BF <1/3 indicates moderate support for H_0 over H_1; BF <1/10 indicates strong evidence for H_0 over H_1; BF = 1 indicates no evidence for H_0 or H_1.

nature research

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Reporting Summary

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☐	☒	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Experimental tasks were run in Psychtoolbox software in Matlab version 2015b. Code is provided at: https://osf.io/e2u73
Data analysis	Data analysis was completed in JASP and R. R code is provided at https://osf.io/e2u73

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

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All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
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All data files are available at: https://osf.io/e2u73

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Quantitative longitudinal study assessing the immediate and longer-term effects of combined decision-making training and transcranial direct current stimulation (tDCS) to the left prefrontal cortex on cognitive function in older adults.
Research sample	Healthy older adult participants aged 60-75 were recruited. Participants were required to have normal or corrected to normal vision and hearing, and to meet the following criteria: (1) No evidence of mild cognitive impairment or dementia (Montreal Cognitive Assessment 26); (2) No current use of psychiatric medication(s); (3) No psychiatric, or neurological condition(s) (e.g., previous stroke, epilepsy); (4) No contraindications to brain stimulation as determined by a tDCS safety screening questionnaire (e.g., metal in the head, implanted neurostimulator, skin conditions of the scalp) and; (5) No clinically significant depressive symptoms (Beck Depression Inventory >13).
Sampling strategy	In adherence to the Bayesian sampling approach, we did not predetermine a sample size for this study. Instead, we recruited participants until Bayes Factors > 10 were established for the critical hypothesis tests, providing strong evidence for the alternative or null hypothesis.
Data collection	Experimental tasks were programmed and completed in Matlab 2015b, using Psychtoolbox software. The Wisconsin Card Sorting Test was purchased from PAR Inc. and run on a PC computer. All questionnaires were downloaded online, except for the BRIEF-A and BDI which were purchased from PAR and Pearson, respectively.
Timing	Data collection commenced on 09/04/2018 and was stopped on 07/11/2019.
Data exclusions	Data from two participants was excluded from analysis, according to the pre-registered protocol, as they missed one or more stimulation sessions.
Non-participation	Two participants withdrew from the study - one due to a headache from tDCS and the second due to illness and difficulty with tasks.
Randomization	Participants were allocated pseudorandomly to one of four stratified groups based on age, gender, education, physical activity.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	129 participants (75 female, mean age = 67.62 ± 4.21 years, mean education = 15.47 ± 3.35 years, 12 participants left handed on the Edinburgh Handedness Inventory)
Recruitment	Recruited via advertisements across multiple media, including television, radio and local newspapers, the University of Queensland (UQ) '50 Plus Registry', staff newsletters and social media, as well as flyers at local community organisations (e.g.

	bowls clubs, retirement villages) and the UQ St Lucia Campus. We emphasised community, rather than university, recruitment in an attempt to achieve a more representative sample of the general population of older adults.
Ethics oversight	UQ Human Research Ethics Committee

Note that full information on the approval of the study protocol must also be provided in the manuscript.