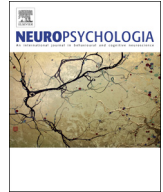




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Modulating fluid intelligence performance through combined cognitive training and brain stimulation

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ABSTRACT

It is debated whether cognitive training of specific executive functions leads to far transfer effects, such as improvements in fluid intelligence (*Gf*). Within this context, transcranial direct current stimulation and recently also novel protocols such as transcranial random noise and alternating current stimulation are being investigated with regards to their ability to enhance cognitive training outcomes.

We compared the effects of four different transcranial electrical brain stimulation protocols in combination with nine daily computerized training sessions on *Gf*.

82 participants were randomly assigned to receive transcranial direct current stimulation (tDCS), random noise stimulation (tRNS), multifocal alternating current stimulation at 40 Hz (mftACS), or multifocal tDCS (mftDCS) in combination with an adaptive and synergistic executive function (EF) training, or to a no-contact control group. EF training consisted of gamified tasks drawing on isolated as well as integrated executive functions (working memory, inhibition, cognitive flexibility). Transfer was assessed with a combined measure of *Gf* including three established tests (Bochumer Matrizen-test - BOMAT, Raven's Advanced Progressive Matrices - RAPM, and Sandia Matrices). We found significant improvements in *Gf* for the tDCS, mftDCS, and tRNS groups when compared with the no-contact group. In contrast, the mftACS group did not improve significantly and showed a similar pattern as the no-contact group. Mediation analyses indicated that the improvement in *Gf* was

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mediated through game progression in the mftDCS and tRNS group. Electrical brain stimulation in combination with sustained EF training can lead to transfer effects in *Gf*, which are mediated by training progression.

1. Introduction

Fluid intelligence (*Gf*), first defined by Cattell (1963), is the ability to cope with novelty, to think rapidly and flexibly, to see relations amongst items independent of acquired knowledge and is predictive of important life outcomes such as income, work performance, and health (Au et al., 2014; Sternberg, 2012). *Gf* is theorized to draw on neural processes that overlap with executive functions (EFs) such as working memory, inhibition, and cognitive flexibility (Bastian and Oberauer, 2014; Burgess et al., 2011; Colzato et al., 2006; Diamond, 2013; Witthöft et al., 2009) as well as the broader concept of creativity (Benedek et al., 2014), and has hence inspired researchers to explore interventions aimed at improving *Gf* via executive function pathways.

Cognitive training of individual EFs such as response inhibition (Enge et al., 2014) or working memory (e.g., Jaeggi et al., 2008; Redick et al., 2013; Rudebeck et al., 2012) has yielded diverging results with regards to transfer effects to *Gf* in healthy subjects. Recent meta-analyses mirror these inconsistent findings in the domain of working memory. While some (Au et al., 2014) support far transfer effects of working memory training to *Gf*, others conclude that working memory training does not “generalize to measures of “real-world” cognitive skills” (Melby-Lervåg et al., 2016). Inconsistent findings have been suggested to partly result from methodological issues (Shipstead et al., 2012) as well as the aggregation of a broad range of test and training tasks. Notably, reported effect sizes for far transfer to *Gf* are mostly small, which leaves the question of how to optimize cognitive training in order to achieve greater transfer effects. One approach is the adaptation of training protocols to imitate more life-like tasks, which commonly require the engagement of several cognitive functions simultaneously. For example, specific EFs are rarely used singularly, but mostly in conjunction with other cognitive functions (Taatgen, 2013). Therefore, training regimes should ideally train multiple functions concomitantly in an effort to imitate real-life challenges.

One potential tool to enhance training outcomes and promote transfer effects is transcranial electrical stimulation (tES). The most prominent form of tES is transcranial direct current stimulation (tDCS), and the latest additions are transcranial alternating current (tACS) and random noise stimulation (tRNS). These techniques do not induce neuronal firing, but rather modulate brain excitability and task-related neuronal activity, which in turn is thought to lead to neuroplastic

changes, and hence physiological mechanisms that are similar to those involved in learning (Cooke and Bliss, 2006; Paulus, 2004; Pelletier and Cicchetti, 2015). Synergistic effects might therefore arise through the combination of cognitive training and tES. A number of studies support the assumption that noninvasive brain stimulation during cognitive training can enhance cognitive functions in healthy subjects (for an overview, see Krause and Cohen Kadosh, 2013; Santarnecchi et al., 2015). These effects might be attributed to stimulation of brain regions that become active during the cognitive training, and therefore to the ability to impact the neuronal substrates of the desired cognitive function more effectively based on the idea of state-dependent brain stimulation (Cohen Kadosh et al., 2010; Feurra et al., 2013; Romei et al., 2016; Silvanto et al., 2007). Moreover, a recent meta-analysis stated that stimulation effects are stronger for training than for performance (Simonsmeier et al., 2018), and theoretical frameworks have been proposed to account for functional enhancement as well as costs (Brem et al., 2014).

Most tES approaches so far have used two stimulation electrodes. However, to increase focus on single brain regions as well as targeting multiple regions of a network, devices are available that allow simultaneous stimulation of multiple brain areas with multiple electrodes (Ruffini et al., 2014). These multifocal protocols differ from recently developed high-definition protocols in that they are not trying to increase focality by suppressing activity in surrounding areas of the region of interest. Furthermore, in comparison to “classic” protocols such as the bifocal tDCS montage, they do not only focus on one brain area that is known to be implicated in a targeted function, but try to modulate a whole network associated with it and therefore imitate “natural” network activation. The optimization of stimulation protocols poses a challenge in this research field. Here we have exploited these recent developments and investigated the combined effects of different tES protocols in combination with cognitive training on *Gf*.

We compared four different stimulation protocols in their efficiency in enhancing *Gf* performance relative to a no-contact group (NC): bifocal tDCS (tDCS), bifocal tRNS (tRNS), multifocal tDCS (mftDCS), and multifocal tACS (mftACS), the latter two being novel protocols developed on the basis of functional imaging literature related to EF (see Methods). Note that our main goal was to compare the different stimulation protocols. The tES methods were applied in combination with a long-term (9 sessions) cognitive training approach integrating several

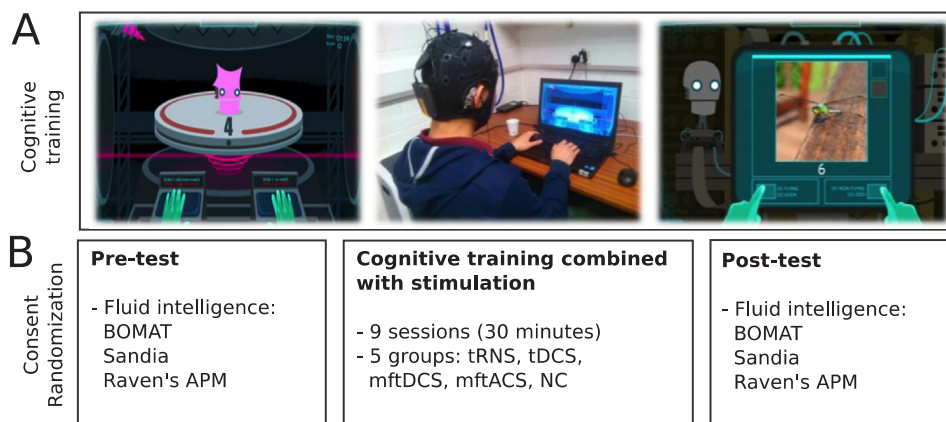


Fig. 1. Cognitive training intervention and study design. A: Cognitive training intervention: The intervention setup is depicted in the top middle panel. Easier cognitive training blocks (top left panel) focus on cues for a single EF task (in this case, matching n-back on numbers). The most difficult blocks (top right panel) contain three EF tasks; in this case, using the background colour to determine when to switch between tasks (switching component) involving matching n-back on number (working memory component) and inhibiting on pictures of flying things that are not birds (inhibition component with a semantic operator). B: Study Design: After consenting and randomization, subjects came in for the pre-test followed by 9 sessions of combined cognitive training and stimulation and the posttest. Subjects randomized to the

no-contact control group attended the pre- and posttest sessions only. Subjects were pretested within 2 weeks before the start of the intervention and post-tested on the day after the last training visit.

EFs concomitantly. We hypothesised that progression in the game would predict *Gf* post, however, we did not preview a hypothesis regarding the predominance of any of the stimulation protocols.

2. Material and methods

2.1. Subjects and study design

In this randomized, controlled, single-blind study eighty-seven healthy subjects (out of ninety-eight enrolled) completed all study procedures. Eleven subjects were excluded from the analysis due to non-compliance with the test administration on at least two independent measures (i.e., > 2 standard deviations). The attrition rate ($n = 11$) was similar across stimulation groups (before intervention: $n = 6$; during intervention: mftACS: $n = 1$, mftDCS: $n = 1$, bitDCS: $n = 2$; bitRNS: $n = 1$). The study took place at two difference sites (University of Oxford and Harvard). The 82 (Oxford $N = 45$; Harvard $N = 37$) were randomized to receive tDCS [$n = 17$, age 28.41 ± 11.58 ; 11 males], mftDCS [$n = 15$, age 27.88 ± 11.58 ; 9 males], tRNS [$n = 16$, age 29.19 ± 10.39 ; 9 males], or mftACS [$n = 17$, age 30.73 ± 13.17 ; 9 males] combined with cognitive training. In addition we included a NC group [$n = 17$, age 30.88 ± 13.30 ; 8 males]. A stratified randomization process taking into account age, education, and gender was applied to control for the influence of these baseline characteristics. Subjects were remunerated for their participation (£10 or \$15 per hour in the UK and the US respectively).

Subjects with any current or past history of psychiatric illness, unstable medical condition, epilepsy or family history of epilepsy, and active or past substance abuse considered a potential hazard for the application of tES were precluded from participating in the study. Subjects were instructed to sleep at least 6 h each night, abstain from alcohol during the entire study duration, and refrain from caffeine for 1 h before study visits. The respective ethics committees (Oxford: NRES Committee South Central – Berkshire; Harvard: CCI/IRB, Beth Israel Deaconess Medical Center) approved the study and all participants gave written informed consent prior to study onset according to the Declaration of Helsinki.

The study design is depicted in Fig. 1. We compared multiple types of stimulation protocols with a NC group in order to assess the most effective regimen. Each training participant received 9 cognitive training sessions on consecutive days (except weekends), each lasting 30 min, combined with one of the four tES protocols. Transfer effects were assessed with a combined measure of three established *Gf* tests, which were assessed before and after the training in a non-randomized approach with the following test sequence: the Bochumer Matrizen-test (BOMAT; Hossiep et al., 1999), Raven's Advanced Progressive Matrices (RAPM (Raven et al., 1998)), and Sandia (www.sandia.gov; Matzen et al., 2010).

2.2. Transcranial electrical stimulation

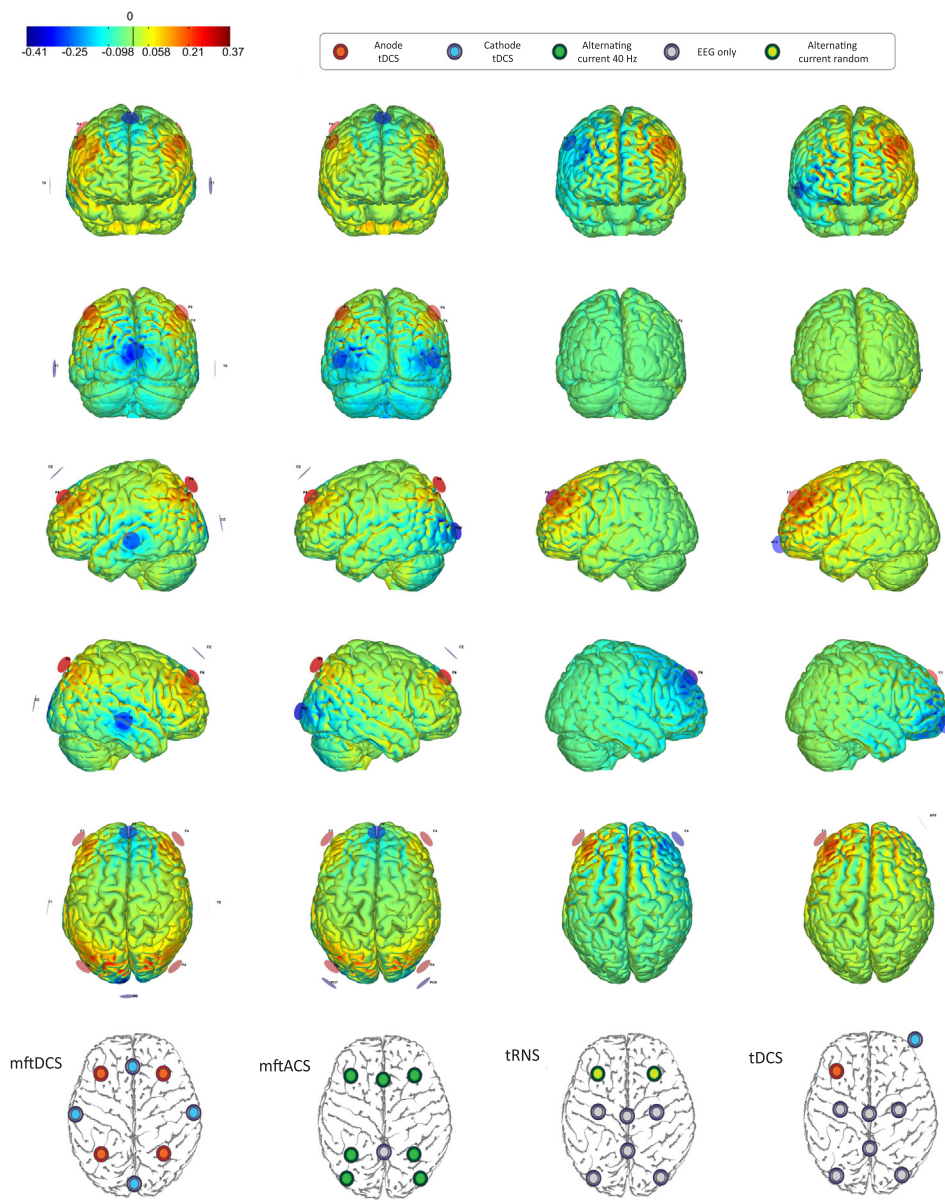
Current was delivered via gel-filled pi-electrodes (3.14 cm^2), which were inserted into a neoprene cap (Starstim®, Neuroelectronics, Barcelona, Spain) in accordance to the international 10–20 EEG system. In all protocols 8 electrodes were mounted (Fig. 2) and spare positions were used to collect EEG data. Stimulation onset coincided with training onset and the current was ramped up and down for the first and last 30 s of stimulation. Participants were monitored at all times to ensure their safety.

TDCS and tRNS are already established stimulation protocols. The chosen parameters were hence based on previous literature that has shown enhancement of various cognitive functions with the specific montages used in the present study (i.e., F3-Fp2 for tDCS and F3-F4 for tRNS), including effects on functions that are strongly related to *Gf* (see Fig. 2 for stimulation details and (Santarnecchi et al., 2015) for a review

on tES to enhance cognition). The amplitude of 1 mA for tRNS implies that 99% of the amplitude values were between $+/- 500 \mu\text{A}$ (Terney et al., 2008). Alternating current stimulation for mftACS was sinusoidal and set to 40 Hz as this frequency was previously shown to modulate complex problem solving (Santarnecchi et al., 2016). The multifocal stimulation templates (mftDCS, mftACS; Fig. 2) were newly developed for the present study through Activation Likelihood Estimation (ALE) analysis (Eickhoff et al., 2012; Turkeltaub et al., 2012) and based on a meta-analysis of imaging literature investigating the three major EFs engaged during FAST with the following tasks: 1) inhibition (go-nogo task, stop-signal task), cognitive flexibility (task switching), and working memory (n-back task, AX version of the continuous performance test). The literature on these functions suggests a more distributed pattern of activation, usually involving both frontal and parietal lobes bilaterally. Studies that did not report MNI/Talairach coordinates, or provided an insufficient description of results or experimental paradigms, were excluded. An average map of all activation foci for each EF was created and a threshold was applied using a False Discovery Rate of .05 (cluster $\text{mm}^3 = 1000$), assuming independence of foci/studies. This average map was used as a seed-region in a following functional connectivity analysis. As expected, a fronto-parietal network was obtained by averaging the fMRI activation maps for each EF and provided the basis for the mftACS and mftDCS protocols (Fischer et al., 2017). These two montages were therefore optimized to focus on bilateral frontal and parietal regions, hereby targeting the entire executive function network, using a genetic algorithm testing any possible combination of electrode positions in the 10–10 EEG system. For the multifocal stimulation protocols we chose tDCS, being the most used enhancement technique, as well as tACS in the gamma band, which was previously shown to be effective in modulating abstract reasoning by our group (Santarnecchi et al., 2013, 2016).

2.3. Cognitive training

Cognitive training (Fig. 1) was presented on a laptop (screen size 17") while subjects listened to custom-designed music and game-specific sounds via earphones. The training consisted of gamified tasks drawing on isolated as well as integrated EFs (working memory, inhibition, and cognitive flexibility). The task setting was a robot factory, in which the participants were employed. They had to work through 2-min task blocks (15 blocks per session), which were preceded by time-limited (30 s) instruction screens, and received feedback on every trial as well as at the end of each block. Difficulty levels were increased whenever subjects passed 80% of a training block, which ensured an individually adapted and constant level of challenge. Reaching a level of 80% correct in a block was considered a successful completion of that block. When a participant reached 50–80% correct in a given block, difficulty would remain the same, while difficulty was decreased when a subject reached < 50% correct. Subjects started with the training of single sub-functions (working memory or inhibition or cognitive flexibility) and continued with combinations of two or all three sub-functions. Subjects never performed the same task twice in a row. At level 1, the trials were differentiated according to stimulus material (numbers, pictures, words, spatial locations) and EF component (working memory, cognitive flexibility, inhibition). At level 2, the trials involved unique pairwise combinations of all three EF components. At level 3, tasks from Levels 1 and 2 were extended to include four logical (*identity*, *AND* and *exclusive*) *OR*). As an example, a task involving exclusive *OR* might require that participants respond only to numbers less than 10 or to purple shapes, but not both. The most difficult training blocks (4a) contained all three EF tasks. For example, one block might consist of two different tasks (switching component), each involving n-back operations (working memory component), as well as a separate cue to not respond (inhibition component). A final, slightly different complexity level (4b) required subjects to partially deduce the rules themselves, as the instructions intentionally obfuscated some information so that



	mftDCS	mftACS (40 Hz)	tRNS	tDCS
1	F3 (anode, 703 μ A)	F3 (675 μ A)	F3 (1000 μ A, 100-500Hz)	F3 (anode, 1250 μ A)
2	Fz (cathode, -1000 μ A)	Fz (850 μ A, 180°)	F4 (1000 μ A, 100-500Hz)	AF8 (cathode, 1250 μ A)
3	F4 (anode, 860 μ A)	F4 (675 μ A)	C3 (EEG)	C3 (EEG)
4	T7 (cathode, -341 μ A)	PO7 (925 μ A, 180°)	Cz (EEG)	Cz (EEG)
5	T8 (cathode, -412 μ A)	PO8 (925 μ A, 180°)	C4 (EEG)	C4 (EEG)
6	P3 (anode, 603 μ A)	P3 (675 μ A)	PO7 (EEG)	PO7 (EEG)
7	P4 (anode, 587 μ A)	P4 (675 μ A)	PO8 (EEG)	PO8 (EEG)
8	Oz (cathode, -1000 μ A)	Pz (EEG)	Pz (EEG)	Pz (EEG)
	30 min	30 min	30 min	20 min

Fig. 2. Stimulation parameters. In all four stimulation protocols (mftDCS, mftACS, tDCS, tRNS) 8 electrodes were mounted and spare positions were used to collect EEG. Stimulation onset coincided with training onset. StimWeaver (Neuroelectronics, Barcelona, Spain) was used to optimize the stimulation montages according to the specified targets (Ruffini et al., 2013). Electric field calculations (component of the electric field orthogonal to the cortical surface E_n [V/m]) were performed using a realistic head model (Miranda et al., 2013). Positive values indicate that the field is directed into the cortical surface. Note that the tRNS and mftACS protocols only depict one instance of stimulation given that polarity changes continually during stimulation.

subjects had to use a trial-and-error approach. For example, the instruction would state that the task contains an inhibition cue, but would not state what this cue consisted of. This regime forces participants to learn general skills rather than training-specific stimulus-response relationships. Difficulty was furthermore increased by reducing the time available to respond, or by increasing the number of items to remember, while changing training parameters in the opposite direction decreased difficulty. Progress in the game was defined as the number of tasks passed of which the participant achieved 80% or better accuracy on the most challenging difficulty level. The development of the cognitive training was effected in collaboration with Simcoach Games (Pittsburgh, PA, USA) and is reported elsewhere (Almquist Norton-Ford et al., in press).

2.4. Gf tests

Gf tests are thought to capture domain-independent nonverbal abilities underlying performance on various cognitive tasks. In the current study, three of the most common tests were administered, which specifically assess logical-deductive reasoning: *BOMAT* (Hossiep et al., 1999), *RAPM* (Raven et al., 1998), and *Sandia* (www.sandia.gov; Matzen et al., 2010). They have a common structure in that stimuli are presented as matrices of patterns in which one pattern is missing. Subjects then have to point out the missing pattern from an array of patterns. The *BOMAT* presents a 5×3 matrix with a choice of 6 possible answers, whereas the *RAPM* and *Sandia* each present 3×3 matrices with a choice of 8 possible answers. Each test was presented for 15 min and subjects were instructed to solve as many of the presented problems as possible.

For the current experiment both the *BOMAT* and the *RAPM* were divided into 2 parallel versions with 14 and 17 stimuli, respectively. Odd and even numbered stimuli were used for *BOMAT*, while we divided the *RAPM* stimuli by approximating an even-odd distribution taking into account item difficulty provided in the test manual. A similar approach has been adopted in previous studies (Jaeggi et al., 2008; Rudebeck et al., 2012; Thompson et al., 2013). The *Sandia* overcomes the issue of a limited number of stimuli by providing the option to choose from a pool of approximately 3000 matrices, obtained through the combination of different stimulus features such as shape, colour and orientation (Matzen et al., 2010). Experimental matrices belong to 4 different classes based on the type and number of analogical operations required for a correct solution (1-, 2-, 3- relations and logic matrices). Parallel versions of the *Sandia* with 42 stimuli each were based on stimuli classes and difficulty levels (Santarnecci et al., 2013, 2016), and presentation time was limited to 1 min per stimulus.

2.5. Statistical analyses

Data was analyzed using SPSS (21.0 for Mac) and the statistical computing software R (2015). Given the nature of our data as a series of successes (correct responses) and failures (incorrect responses or items not attempted), we modeled subjects' performance on Gf tests as a binomial process, employing a logistic regression analysis approach. In this analysis, outcome variables were the binomial distribution of correct and incorrect responses from each participant at posttest defined by the total number of items on the tests. We modeled subjects' accuracy across all Gf tests at posttest, given their (1) experimental condition (mftACS, tDCS, mftDCS, tRNS, NC), (2) baseline ability in all Gf tests, and (3) age. We used the general linear model (GLM) function to estimate the logistic regression model. In this case, the linear predictor was associated to the outcome with the link function logit. In the first equation the reference category for Condition was NC. In a post-hoc analysis we used the stimulation group with the weakest effect as the reference category to further shed light on the current effect, and the differences between the groups.

We further clarify whether progression in the game was mediating

Gf post in the different stimulation groups by conducting a mediation analysis [bootstrapped with 10,000 samples and 90% confidence intervals (CIs) given the directional hypothesis between progress in the game and improved Gf] in each of the stimulation groups using the PROCESS module in SPSS (Hayes, 2013). In order to integrate the different Gf measures, we aggregated the standardized scores of the three Gf tests at pre- and posttest. The mediation analysis verified whether the effect of an independent variable (X, in this case Gf pre) on a dependent variable (Y, Gf post), denominated c path, is mediated by a mediator variable (M, game progression). The c path corresponds to the beta regression coefficient of the linear regression with Y as dependent variable and X as predictor. The connection between the independent variable (X) and the mediator (M) is a denominated a path, whereas the connection between the mediator (M) and the dependent variable (Y) is a denominated b path. The a path corresponds to the beta coefficient of the linear regression with the mediator (M) as outcome variable and the independent variable (X) as predictor. The b path, instead, corresponds to the beta coefficient of the linear regression with the dependent variable (Y) as outcome and the mediator (M) as predictor when the contribution of the independent variable (X) is controlled by including it into the model. Therefore the mediation analysis can elegantly demonstrate a link between several variables in our experiment. The product of the a and b paths represents the indirect effect of the independent variable (X) on the dependent variable (Y) through the mediator (M) and its significance is evaluated adopting a resampling technique to obtain a bootstrapped distribution of ab products. Despite the a and b paths may be themselves statistically significant, a robust way to establish a specific indirect effect of the independent variable (X) on the dependent variable (Y) through the mediator (M) is to observe when the 90% CIs of the bootstrapped distribution of the ab products does not overlap zero (Hayes, 2013; Hayes and Scharkow, 2013). The mediation model can elucidate the role of game progression, which was hypothesised to act as a mediator in the relationship between the predictor X (Gf pre) and the outcome Y (Gf post). In this respect mediation analyses allow a better view of the mechanisms of change due to the intervention (Fairchild and MacKinnon, 2009). In addition, the mediation analysis allows us to examine several hypotheses within one analytic framework. That is, the a path allows us to examine the link between pre Gf and training progression, as would be predicted by current theories (Diamond, 2013), unless stimulation might alter this expected relationship. The b path allows us to examine if progression in the cognitive training is transferred to post Gf scores, while controlling for baseline (pre) Gf.

3. Results

At baseline, groups did not differ significantly with regards to age ($F(4,81) = .21, p = .934, \eta_p^2 = .01$), gender ($\chi^2(4, N = 82) = 1.68, p = .795$), and education ($F(4,81) = .50, p = .736, \eta_p^2 = .03$). As expected, education was positively associated with baseline Gf [controlling for age] ($r = .261, p = .038, 95\% \text{ CI } [.03, .48]$). However, education was negatively correlated with the change in Gf [controlling for age] ($r = -.327, p = .008, 95\% \text{ CI } [-.57, -.01]$) indicating that subjects with lower education showed a higher increase in Gf over all cognitive training groups.

No major side effects were reported and all stimulation groups showed similar progress (number of tasks where subjects achieved 80% or better accuracy) in the training ($F(3,63) < 1, p = .818, \eta_p^2 = .08$).

3.1. Logistic regression

In a first model, the reference category for Condition was NC (Table 1, model 1). We found that all stimulation protocols, except the mftACS ($p = .510$) protocol, improved significantly more in Gf after the training intervention (all $p_s < .05$).

In a second model we then chose the weakest stimulation group

Table 1
Logistic regression analysis of subjects' accuracy across all *Gf* tests.

Independent variable	b	se	z ratio	p
Model 1^a (Compared to NC)				
mftACS	.057	.086	.66	.510
mftDCS	.235	.088	2.67	.008
tDCS	.239	.086	2.79	.005
tRNS	.212	.086	2.46	.014
Model 2^b (Compared to mftACS)				
NC	-.057	.086	-.66	.510
mftDCS	.179	.088	2.03	.043
tDCS	.182	.083	2.19	.029
tRNS	.156	.085	1.83	.067

^a *Gf* baseline: $b = .050$ ($SE = .005$), $p < .001$; Age: $b = -.025$ ($SE = .003$), $p < .001$.

^b *Gf* baseline: $b = .050$ ($SE = .005$), $p < .001$; Age: $b = -.025$ ($SE = .003$), $p < .001$.

(mftACS) as reference category (Table 1, model 2). This model showed that the mftACS group was performing significantly weaker than the tDCS group ($p = .029$) and the mftDCS group ($p = .043$), and marginally weaker than the tRNS group ($p = .067$). Furthermore, we found a significant negative correlation between age and *Gf* scores at pretest ($r = -.592$, $p < .001$, 95% CI $[-.71, -.44]$) as well as posttest ($r = -.562$, $p < .001$, 95% CI $[-.70, -.39]$). However, the change in *Gf* score was not correlated with age ($r = -.150$, $p = .178$, 95% CI $[-.40, .11]$).

3.2. Mediation analyses

Mediation analyses elucidate the mechanisms that are hypothesised to underlie the relationship between independent and dependent variables (changes from pre- to post-training *Gf* scores), via the inclusion of an explanatory variable - the mediator variable (progression in the game). As expected, regressing *Gf* post onto the *Gf* pre (*c* path) resulted in a significant association between the variables in all groups (all $ps < .001$). Participants with a high *Gf* pre score were therefore more likely to achieve a high *Gf* post score. We then entered the mediator, progression in the game, into the model.

For the mftACS group (Fig. 3), *Gf* pre was not significantly associated with progression ($p = .125$). Similarly, progression was not significantly associated with *Gf* post ($p = .29$). The bias-corrected bootstrapped confidence interval for the specific indirect effect of the mapping of *Gf* pre on *Gf* post through progression crossed zero (.02, 90% CI $[-.02, .24]$).

For the tDCS group (Fig. 3), *Gf* pre was significantly associated with progression ($p < .001$). However, progression was not significantly associated with *Gf* post ($p = .14$). The bias-corrected bootstrapped confidence interval for the specific indirect effect of the mapping of *Gf* pre on *Gf* post through progression crossed zero (.22, 90% CI $[-.23, .64]$).

For the mftDCS group (Fig. 3), *Gf* pre was significantly associated with progression ($p = .045$). Progression, in turn, was significantly associated with *Gf* post ($p = .003$). The bias-corrected bootstrapped confidence interval for the specific indirect effect of the mapping of *Gf* pre on *Gf* post through progression remained above zero (.21, 90% CI $[.02, .46]$) indicating a significant mediation effect.

For the tRNS group (Fig. 3), *Gf* pre was significantly associated with progression ($p = .01$). Progression was also significantly associated with *Gf* post ($p = .028$). The bias-corrected bootstrapped confidence interval for the specific indirect effect of the mapping of *Gf* pre on *Gf* post through progression remained above zero (.16, 90% CI $[.03, .47]$) indicating, again, a significant mediation effect.

These results support an indirect effect of *Gf* pre on *Gf* post through the progression in the game for the groups receiving mftDCS and tRNS. Interestingly, mediation effects in the tDCS group did not reach

significance, even though coefficients were high and their pattern similar to the mftDCS and tRNS groups. This could be explained by increased variance in the *b* path in this group compared to the others.

4. Discussion

This study compared four tES protocols with sustained 9-session integrative EF training in terms of transfer to *Gf*. Although we observed greater improvements in *Gf* for three protocols (tRNS, tDCS, mftDCS) compared to NC, mftACS did not demonstrate similar benefits.

In order to elucidate underlying mechanisms, we investigated the mediating role of game progression in *Gf* outcome. Notably, game progression only mediated *Gf* outcome in the groups that received mftDCS or tRNS; though the tDCS group showed a similar pattern with similar effect size.

This study did not include a sham group or an active control group, which could have elucidated the specific contribution of cognitive training alone, which was not the aim of the current study, but rather to compare the differential effects of the four stimulation protocols. However, it is known that cognitive training alone shows small transfer effects to *Gf* (Jaeggi et al., 2011). Given that transfer effects were observed for the tRNS and mftDCS groups, we doubt that such transfer effects might be epiphenomena, induced by other factors, such as motivation, remuneration, or the so-called 'Hawthorne effect' (the interaction with the experimenters). Previous studies have already revealed

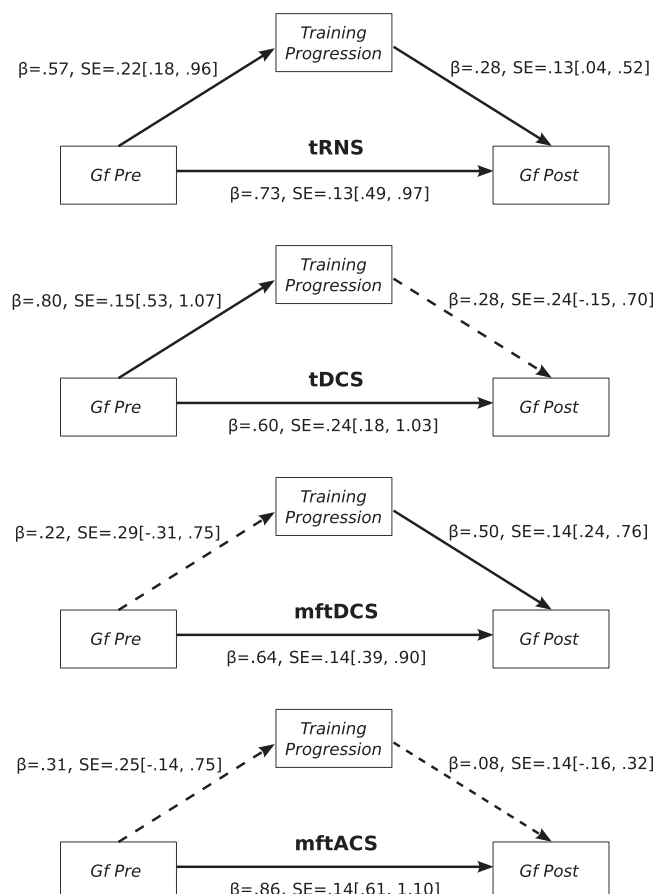


Fig. 3. Mediation analyses to examine whether the relation between pre- and posttest *Gf* is mediated by game progression in each stimulation group. Standardized regression coefficients, standard errors, and 90% confidence intervals (in parentheses), bootstrapped with 10,000 resamples are reported. Solid lines indicate significant paths. Due to our directional hypothesis based on previous literature (Au et al., 2014; Jaeggi et al., 2008; Taatgen, 2013) these are one-tailed tests.

long-term transfer with tRNS (Cappelletti et al., 2013; Snowball et al., 2013). Using a similar stimulation protocol, Snowball and colleagues (Snowball et al., 2013) demonstrated that behavioural improvements were associated with hemodynamic responses specifically within the left DLPFC, although the exact mechanisms of tRNS-related effects in the current study might differ.

As the mftDCS protocol is a novel approach, we can only speculate about the underlying mechanisms. We suspect that simultaneous stimulation of brain areas that are relevant for the trained EF, specifically frontal and parietal areas, buttressed any advantageous effects.

Electric field modelling was used to ensure that indeed the intended areas were stimulated whilst reducing shunting effects due to mounting several (though small) electrodes in relatively close proximity. The application of only one frequency (40 Hz) of alternating currents over several brain regions in our mftACS protocol, however, may not be sufficient to account for the complex interplay of oscillatory activity in these brain areas and possibly even had a detrimental effect on training outcome. It is premature, based on one stimulation protocol, to conclude that mftACS cannot be effective for cognitive learning and transfer, and future studies will need to further examine the effect of alternative montages, different timing of stimulation with regard to the training (online vs. offline), frequencies, or amplitudes on behavioural outcomes. Importantly, even though the present montage was optimized to homogeneously distribute current intensity across the electrode array, the phase of oscillatory stimulation was not completely balanced due to physical constraints induced by the proximity of some electrodes. Given the relevance of phase information for tACS applications (Polanía et al., 2012), this might have constituted an undesired source of noise and should be carefully addressed in future investigations.

It should be noted that multifocal solutions allow for stimulation of a larger number of regions, approximating stimulation of entire cortical networks. However, given the limitation in overall stimulation intensity imposed by tES safety guidelines, solutions including more than two electrodes usually result in a more distributed but lower stimulation intensity, which might in turn result in a sub-threshold stimulation. This could apply to both the mftDCS and the mftACS protocol. Moreover, given that mftACS effects might be driven by both local entrainment of specific oscillatory activity as well as by synchronization of different areas via in-phase stimulation (i.e., 0 degrees phase difference between stimulation electrodes), the mftACS protocol used in the present study might have elicited desynchronization of the targeted fronto-parietal network, thus inducing segregation of activity in frontal and parietal regions.

Finally, age was negatively correlated with pretest as well as posttest *Gf*, but the change in *Gf* was independent of age. Previous studies in young healthy adults have shown that subjects with lower baseline abilities may profit more from brain stimulation interventions aiming to improve cognitive functions (Foroughi et al., 2014; Hsu et al., 2014; Liang et al., 2014; Looi et al., 2016; Tseng et al., 2012). Lower functioning subjects should have a higher margin for improvement, as there is room for optimization of cognitive processes, while higher functioning subjects already perform at an optimal physiological level, which might prevent further improvement (Brem et al., 2014; Hsu et al., 2014; Krause et al., 2013). However, with advancing age, functional and structural changes might, in return, modify underlying mechanisms and lead to differential outcomes (Berryhill and Jones, 2012; Learmonth et al., 2015; Li et al., 2015). Recent research suggests that individual traits and momentary state predict behavioural outcomes after stimulation (Benwell et al., 2015; London and Slagter, 2015; Sarkar et al., 2014). Future studies should address the question of whether cognitive training combined with brain stimulation might lead to an assimilation of high and low functioning individuals by targeting low functioning individuals more effectively.

In sum, after nine sessions of brain stimulation combined with cognitive training we found transfer effects to *Gf* measures for the

mftDCS and tRNS groups. Future studies should explore whether individualized intervention protocols based on trait (e.g., age, education, genetic polymorphisms) and momentary state can enhance individual training effects.

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Conflict of interest statement

RCK serves on the scientific advisory boards for InnoSphere Inc., The Cognitive Enhancement Foundation (non-profit organization), and Neuroelectronics Inc. APL serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectronics Inc., Axilum Robotics, Magstim Inc., and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging. The authors declare no competing interests and do not hold any interests in the training software or Simcoach Games beyond scientific interest.

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