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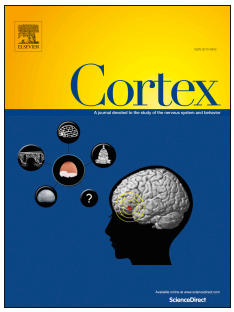

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Individual Differences and Specificity of Prefrontal Gamma Frequency-tACS on Fluid Intelligence Capabilities.

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Abstract

Emerging evidence suggests that transcranial alternating current stimulation (tACS) is an effective, frequency-specific modulator of endogenous brain oscillations, with the potential to alter cognitive performance. Here, we show that reduction in response latencies to solve complex logic problem indexing fluid intelligence is obtained through 40Hz-tACS (γ-band) applied to the prefrontal cortex. This improvement in human performance depends on individual ability, with slower performers at baseline receiving greater benefits. The effect could have not being explained by regression to the mean, and showed task and frequency specificity: it was not observed for trials not involving logical reasoning, as well as with the application of low frequency 5Hz-tACS (theta band) or non-periodic high frequency random noise stimulation (101-640Hz). Moreover, performance in a spatial working memory task was not affected by brain stimulation, excluding possible effects on fluid intelligence enhancement through an increase in memory performance. We suggest that such high-level cognitive functions are dissociable by frequency-specific neuromodulatory effects, possibly related to entrainment of specific brain rhythms. We conclude that individual differences in cognitive abilities, due to acquired or developmental origins, could be reduced during frequency-specific tACS, a finding that should be taken into account for future individual cognitive rehabilitation studies.

Keywords: cognitive enhancement; fluid intelligence; individual differences; non-invasive brain stimulation; transcranial electrical stimulation; tACS

Introduction

High level cognitive processes such as consolidation of episodic memory traces (Marshall, Helgadottir, Molle, & Born 2006), working memory (WM) (Polania, Nitsche, Korman, Batsikadze, & Paulus 2012), decision making (Sela, Kilim, & Lavidor 2012) and logical reasoning (Santarnecchi et al. 2013a) may benefit from noninvasive transcranial alternating current stimulation (tACS), particularly when the applied frequency coincides with the endogenous regional synchronization that accompanies the function of interest. These findings confirm experimental evidence indicating that tACS induces a reinforcement of ongoing brain oscillations by "entrainment" (Frohlich and McCormick 2010;Reato, Rahman, Bikson, & Parra 2010) or "resonance" phenomena of large-scale networks (Ali, Sellers, & Frohlich 2013a;Antal and Paulus 2013), an effect that might be exploited for rehabilitative or enhancement interventions with tACS in humans (Santarnecchi et al. 2015).

Whether tACS-induced cognitive enhancement takes place irrespective of pre-stimulation individual differences in performance (and-or underlying neurophysiological dynamics), or alternatively, depends on the individual's cognitive and-or oscillatory patterns profile, is still unknown. However, the latter scenario might better align with the documented state-dependency of tACS effect on the motor and visual systems, which suggests how the response to tACS is modulated by behavioral demands and consequently by the neurophysiological changes accompanied by these (Feurra, Pasqualetti, Bianco, Santarnecchi, Rossi, & Rossi 2013;Kanai, Chaieb, Antal, Walsh, & Paulus 2008). If this were the case, the dependency on individual cognitive -as well as purely neurophysiological- profile might represent a key feature in determining the potentials (and limits) for neuroenhancement applications.

In a previous study (Santarnecchi et al. 2013a), 40Hz-tACS (gamma-band) has been applied to the prefrontal cortex during a fluid intelligence (G*f*) task, which includes logic reasoning problems and relational problems. Briefly, logic reasoning refers to the ability to solve problems based on logical conditional arguments (e.g. where specific rule of inference "Modus Tollens" is applied: *if P then Q; not-Q*; e.g. "if there is a circle then there is a triangle. There is not a triangle. Therefore, there is not a circle"; see Figure 1 A - Logic), which have been demonstrated to mostly activate prefrontal structures (Prado, Van Der Henst, & Noveck 2010). On the other hand, relational problems are based on perceptual relations (i.e. linear arguments as those in relational syllogisms, e.g. *P is to the left of Q; Q is to the left of R*; "The circle is to the left of the triangle. The triangle is to the left of the square. Therefore, the circle is to the left of the square"; see Figure 1 A - Relational) and require less prefrontal engagement in favor of higher parietal activation (Prado, Van Der Henst, & Noveck 2010). By comparing 40Hz tACS with other stimulation frequencies (5Hz, 10Hz, 20Hz) and a Sham condition, Santarnecchi et al. (2013a) found a trial type-specific decrease in the time required to solve complex logic reasoning problems in healthy subjects. However, it is still unclear whether improvements in logic reasoning may occur as (1) a consequence of the modulation of brain dynamics leading to a change of cortico-spinal excitability –instead of a specific modulation of the brain rhythm(s) being targeted— or (2) as an indirect enhancement of other cognitive functions, such as WM, which is an integral part of G*f* abilities (Diamond 2013). Moreover, given the positive correlation between G*f* and performance on a wide range of cognitive tasks, as well as its role as a predictor of both educational and professional success (Baltes, Staudinger, & Lindenberger 1999;Gottfried, Fleming, & Gottfried 1998), understanding the role of individual cognitive

differences in the response to tACS represents an important question for future application as well.

We tested these hypotheses in two experiments by applying different stimulation parameters, and during performance on a visuospatial WM task and a visuospatial abstract reasoning task commonly used for indexing G*f*.

Materials and Methods

Participants

Participants were healthy right-handed individuals recruited from the University of Oxford vicinity. Fifty-eight subjects were included, after being screened for overt contraindications for transcranial electrical stimulation (tES), including personal and family history of epilepsy, unstable medical conditions, psychoactive or central nervous system-active medication, and recent migraine attacks. Twenty-four individuals (11 female) (23.8 ± 3.14 years) took part in Experiment 1, thirty-four individuals (17 female) (24.3 ± 2.76 years) took part in Experiment 2 (Gender, $\chi^2 = 0.98$, $p > 0.75$; Age, $t_{(56)} = -0.88$, $p > 0.61$). All participants provided written informed consent. Participants were compensated with £30 for their time. The study was approved by the Berkshire Ethics Committee (10/H0505/72).

Experimental Paradigm

The aim of Experiment 1 was twofold: (i) testing for the effect of different tACS frequency on G*f* performance, as well as (ii) the potential concurrent effect of tACS on WM performance(see Fig. 1). Twenty-four participants performed G*f* and WM tasks (see the following paragraphs for a detailed description) while receiving 40 Hz (γ), 5 Hz (θ) or sham-tACS in a fully counterbalanced design (both task and stimulation order). In Experiment 2 (n=34), we used the same experimental design, but replaced stimulation in θ band with high-frequency transcranial random white noise (101-640Hz) stimulation (tRNS). This allowed us to examine the role of frequency-specific resonance phenomena and potential modulation of cortical excitability as the mechanism of action for tACS-induced G*f* improvement, since tRNS is assumed to alter brain dynamics in a way that cortical excitability is modified (see below). Moreover, it also allowed replicating the findings from Experiment 1 in respect to individual differences and the role of WM.

High-frequency tRNS is a recently developed form of transcranial electrical stimulation (tES) based on a random (i.e., not sinusoidal) electrical oscillatory spectrum (101-640Hz), capable of inducing long-lasting effects on cortical excitability when applied on the scalp overlying the motor cortex (Terney, Chaieb, Moliadze, Antal, & Paulus 2008) and the dorsolateral prefrontal cortex (Snowball et al. 2013). In contrast to tACS, where a single-frequency signal is delivered, tRNS relies on a multi-frequency signal. Previous studies have suggested that tRNS modifies the inherent signal-to-noise ratio of the targeted brain region (Chaieb, Paulus, & Antal 2011) via stochastic resonance (Fertonani, Pirulli, & Miniussi 2011). In both Experiments 1 and 2, both types of stimulation were set for 30 minutes, while sham

stimulation was set for 30 seconds. Stimulation was terminated as soon as the participant completed the set of matrices, and was followed by a break.

Stimulation parameters: For tACS, sinusoidal stimulation with no DC offset was delivered at an intensity of 750 μA (peak-to-peak), with an average current density at the stimulation electrode equal to ~30 $\mu A/cm^2$. This stimulation intensity was chosen to avoid flickering at the periphery of the visual field typically reported by participants at higher stimulation intensities (Paulus 2010; Terhune, Song, & Cohen Kadosh, 2015). Sham blocks were composed of 30 seconds of tACS using the frequency of stimulation applied in the previous block. Participants reported mild tingling sensations only at the beginning of the stimulation. Only 2 out of 58 participants reported flickering at the periphery of their visual field during 40 Hz tACS in Experiment 1. Transcranial stimulation was delivered through a battery-driven stimulator (Eldith DC-Stimulator, NeuroConn, Germany), connected to conductive-rubber electrodes, and covered in sponges (5x5cm). Sponges were saturated in saline to keep impedances below 10 kΩ throughout stimulation sessions, thereby minimizing cutaneous sensations.

Targeting the Stimulation site: In both experiments we targeted the left middle frontal gyrus (MFG) and used the vertex (Cz in the 10-20 EEG system) as the return electrode (Fig. 1C). We chose the left MFG based on a previous study (Santarnecchi et al. 2013a). The procedure for subject-wise hotspot identification was been conducted with Munster T2T software (http://wwwneuro03.uni-muenster.de/ger/t2tconv/). Starting from inion-nasion and tragus-tragus distance estimation, we identified the vertex and located electrode positions by moving through the *x* and *y* planes.

Task Overview: To estimate G*f* abilities we used a modified, computer-based version of Raven's Matrices, a visuospatial abstract reasoning task widely used to index G*f* (Matzen, Benz, Dixon, Posey, Kroger, & Speed 2010). To measure visuospatial working memory (WM), we employed a standard change localization task in which participants selected which one of four squares differed on their second presentation with respect to the first. These two tasks, presented sequentially with a one-minute break between them, constituted a single block. After a short training session, participants performed three blocks, receiving a different form of tES in each. There was a 24-minute break between blocks, with a twofold purpose: 1) to allow participants to rest; and 2) to minimize carry-over effects of stimulation, as some short-term, post-tACS after-effects have been reported. Notably, this has been noted in the alpha frequency range and only after prolonged stimulation sessions (Zaehle, Rach, & Herrmann 2010). Between blocks, and before the first and after the last block, participants completed a short, low cognitive-load control task, requiring them to classify a series of numbers appearing on the screen as odd or even. Participants were instructed to respond as fast and as accurately as possible in all tasks. They were informed before the start of the experiment that the participant with the highest number of correct matrices would receive a bonus prize of £20. This was to incentivize participants to respond as accurately as possible and remain focused throughout the experiment. The full experiment lasted approximately 3 hours per participant. All experiments were presented using E-prime 1.2 software (Psychology Software Tools, Pittsburgh, PA).

Task descriptions: Abstract-Reasoning task. Participants performed a PC-based version of Raven's Matrices, i.e. the Sandia matrices (Matzen, Benz, Dixon, Posey, Kroger, & Speed 2010). Respect to the original Raven stimuli, the Sandia tool includes multiple sets of validated

stimuli which thus allow for repeated measurement of G*f*, also allowing for sensitive recording of response times (Santarnecchi et al. 2013a). Each matrix was composed of a 3x3 grid, with each cell in the grid containing a set of shapes. There was a blank cell in position 3–3 of the grid (bottom right). The participant was required to complete the matrix using one of eight options (Figure 1). Participants responded by pressing the corresponding key on a keyboard. A maximum of 60 seconds was allowed for each matrix, after which the next matrix appeared. Two different sets of matrices were presented: Relational matrices and Logic matrices, corresponding to different cognitive operations discussed above. Relational matrices could be solved by capturing variations in the features of shapes across cells in the grid, (i.e. colour, size, orientation, number, shape), with some features stay constant while others vary. In contrast to Santarnecchi et al. (2013a) only the highest difficulty was used, with variation in three of the five features, referred to as "three-relations" matrices. This was done in order to reduce the total experiment time, and because these matrices are relatively easy to solve (Santarnecchi et al. 2013a). Logic matrices required participants to perform logical operations across the matrix (i.e. conjunction, disjunction, or exclusive disjunction, known as AND, OR and XOR functions, respectively), similarly to the conditional inferences discussed above. Logic and relational matrices were presented in a randomized order, and the interstimulus interval was five seconds. Additionally, before starting the first block, participants performed a short training exercise to familiarize with the stimuli and reduce possible novelty effects in the first block. The training exercise consisted of 48 matrices, 12 belonging to each category of Logic matrices and one-, two- and three-Relational. The easy-to-solve one and two Relations matrices were included in the training block in order to prevent discouraging participants due to task difficulty. Before starting the training block, brief verbal instructions were given to participants explaining the

task. After the first twelve matrices, a screen presented additional experimental instructions: this screen explained that there were two types of trials (relational and logic), and explained how to solve them (by looking for changes in features across the matrix, or by performing a logical operation, respectively). We confirmed verbally that participants understood the task and how to solve the matrices. Giving detailed instructions to assist participants in solving the matrices was crucial, as we aimed to maximize the number of correct responses and minimize the effect of practice across blocks. Indeed, it was important to collect the highest number of correct responses, since the effect of interest was a modulation of response times on correct responses rather than accuracy (Santarnecchi et al. 2013a). After these more detailed instructions, participants completed the remainder of the training block. In both experiments, there were 12 trials of both Relational and Logic (24 matrices per block, 72 matrices in total, with each matrix appearing for 60 seconds), presented in a randomized order. To ensure proper counterbalancing between groups and within conditions, both normative correct responses for each matrix (expressed as percentage scores) and specific types of analogical operations required to solve them (changes in shape, size, orientation, number of stimuli, and transformation direction [horizontal, vertical, outward, diagonal]) were factored into the study design.

Task descriptions: WM task. To assess visuospatial WM, we used a delayed-match-to-sample, change-localization task requiring participants to detect which one of four squares changed color between the first and second presentation of a set of four squares (Luck and Vogel 1997). Participants were instructed to fixate on a cross in the middle of the screen at the start of a trial. Four squares briefly (100ms) appeared around this fixation cross (one in each quadrant). After a short interval (800ms), four squares reappeared in the same locations. One of the squares,

randomly selected, would changed color (Figure 1). The squares corresponded to a size of approximately 1.1 degrees of the visual angle, and would appear approximately 5.5 degrees of the visual angle around the fixation cross. A color change of one square occurred on every trial and no two squares on the screen at the same time would be the same color. Participants used the mouse to click on the differently-colored square. The second set of squares remained on the screen until participants responded. Again, accuracy and response times were recorded. After selecting a response, the next trial would begin. There were 60 trials in each block. A 30-second break was provided halfway through the task.

Task descriptions: Control task. The control task consisted of classifying 100 randomly generated numbers presented sequentially on the computer screen as odd or even. A fixation cross would appeared on the screen for 1 second followed by a randomly generated number between 1 and 99. Participants then responded using a key press to specify whether the number was odd or even. Accuracy and RT were recorded. This acted as a control task to assess attention/vigilance/fatigue by detecting any changes in reaction time (RT) and accuracy over the course of the experiment or any potential general after-effects of stimulation on RTs and accuracy.

Data Analysis

Analyses were carried out using IBM SPSS Statistics (Version 21, release 21.0.0) and MATLAB (Release 2012b, Mathworks). Both Experiment 1 and 2 were analyzed in the same manner. Data were filtered for outliers (mean ± 2SD, 6% of the trials). RTs and accuracy data were investigated for both the Sandia Matrices task and the WM task. In terms of factors, Sandia

Matrices included the relational and logic trials, which along with WM trials, gave three trial types in total. To investigate main effects and interactions of stimulation and trial type in Experiment 1 and 2 for both correct RTs and accuracy, a three-way repeated measures ANCOVA with the stimulation type (sham, 40Hz-tACS, and either 5Hz-tACS for Exp 1 or tRNS for Exp 2) and trial type (Logic, Relational and WM) as within-subjects factors. Gender, the order of task (Sandia matrices/WM) and the order of the stimulation conditions were added as covariates. In the event of a significant effect of stimulation, further simple main effects were analyzed using a similarly structured ANCOVA to decompose the effect. In the event of an interaction between stimulation and trial type and a subsequent significant simple main effect of stimulation on a specific trial type, pairwise comparisons were performed to elucidate the nature of the effect. In the event of a violation of Mauchly's test of sphericity, we employed multivariate measures, which are not limited by the sphericity assumption. We performed correlation analyses by carrying out Pearson product-moment correlation coefficient between the variables of interest, again by controlling for the effect of order for task, stimulation and gender. Speed-accuracy trade-offs were examined using partial correlations and repeated measures ANCOVAs, similar to those described above. Principle components analysis was performed on z-score adjusted data to account for differences across trial types. For all tests the level of significance was set at $p \leq 0.05$.

Results

Experiment 1

Response time. This analysis revealed a significant effect of stimulation [$F_{(2,19)}$ = 5.20, p<0.01, Cohen's d = 0.53] and trial type [$F_{(2,19)}$ = 12.67, p<0.001, Cohen's d = 1.42], as well as a significant stimulation×trial type interaction [$F_{(4,17)}$ = 10.11, p<0.001, Cohen's d = 0.62]. Simple main effects of stimulation for each trial type were analyzed separately. The simple main effect for stimulation was significant for Logic trials [$F_{(2,19)}$ = 15.91, p<0.001, Cohen's d = 0.74], marginally significant for Relational trials [$F_{(2,19)}$ = 3.08, p=0.069, Cohen's d = 0.42], and non-significant for the WM task [$F_{(2,19)}$ = 0.43, p=0.653]. Therefore, the most likely source of the stimulation×trial type interaction was due to a different effect of stimulation on WM compared to Logic and Relational trials. To test this, a trend analysis (Logic = Relational ≠ WM) was applied. This analysis revealed a significant stimulation×trial type interaction [$F_{(4,17)}$ = 23.93, p<0.001, Cohen's d = 0.98], confirming that the source of the interaction was the WM task.

To further explore the interaction between stimulation and trial type we investigated the significant effect of the tACS condition on Logic and Relational trials separately. In the case of Logic trials, RTs for correct responses on the 40Hz-tACS condition were significantly faster compared to both sham [$t_{(23)}$ = 5.84, p<0.001, Cohen's d = 0.98] and 5Hz [$t_{(23)}$ = 3.57 p<0.01, Cohen's d = 0.78] stimulation (Figure 2). Five-Hz tACS and sham were not significantly different [$t_{(23)}$ = 0.51, p=0.613]. The mean reduction in response time during 40Hz-tACS compared to the sham condition was 3.6s, corresponding to a 21% decrease of the time required to correctly solve Logic matrices. In the Relational trials, response times during 40Hz-tACS were not significantly faster compared to sham [$t_{(23)}$ = 1.12, p<0.198] and 5Hz-tACS [$t_{(23)}$ = 1.24, p=0.228]. (Figure 2).

Accuracy. While a significant main effect of stimulation was not observed [$F_{(2,19)}$ = 1.02, p=0.380], a significant main effect of trial type [$F_{(2,19)}$ = 4.52, p<0.05, Cohen's d = 0.45], and a significant stimulation×trial type interaction [$F_{(4,17)}$ = 4.36, p<0.05, Cohen's d = 0.37] emerged. Further decomposition of this interaction for each trial type revealed no significant effect of stimulation on accuracy for Logic [$F_{(2,19)}$ = 2.56, p=0.103], Relational [$F_{(2,19)}$ = 2.03, p=0.159] or WM trials [$F_{(2,19)}$ = 0.003, p=0.997] (Figure S1, S2).

Experiment 2

Response times. A significant main effect of stimulation [$F_{(2,29)}$ = 7.45, p=0.002, Cohen's d = 0.54] and trial type [$F_{(2,29)}$ = 32.45, p<0.001, Cohen's d = 0.89] were identified, while the interaction between stimulation and trial type did not reach significance [$F_{(4,27)}$ = 1.00, p=0.411]. As for Experiment 1, simple main effects of stimulation for each trial type were analyzed separately. The simple main effect for stimulation was significant for Logic trials [$F_{(2,29)}$ = 22.56, p<0.001, Cohen's d = 0.81], while non-significant for Relational trials [$F_{(2,29)}$ = 1.32, p=0.237, Cohen's d = 0.28] and the WM task [$F_{(2,29)}$ = 0.64, p=0.544]. RT for correct Logic trials during 40Hz-tACS condition were significantly lower compared to both sham [$t_{(33)}$ = 5.12, p<0.001, Cohen's d = 0.75] and tRNS [$t_{(33)}$ = 3.39 p<0.01, Cohen's d = 0.56] (Figure 2). Sham and tRNS were not significantly different [$t_{(33)}$ = 0.632, p=0.531]. The mean reduction in response time during 40Hz-tACS compared to the sham condition was 3.2s, corresponding to a 19% decrease of the time required to correctly solve Logic matrices. In the Relational trials, response times during 40Hz-tACS were not significantly faster compared to sham [$t_{(33)}$ = 0.89, p<0.347] and tRNS [$t_{(33)}$ = 0.81, p<0.410] (Figure 2).

Accuracy. The only significant main effect was for stimulation [$F_{(2,29)}$ = 6.73, p<0.01, Cohen's d = 0.52; trial type: $F_{(2,29)}$ = 0.91, p=0.413]. In addition, there was a significant stimulation×trial type interaction [$F_{(4,27)}$ = 8.14, p<0.01, Cohen's d = 0.59]. Further decompositions of this effect demonstrated a significant simple main effect of stimulation on Logic accuracy [$F_{(2,29)}$ = 3.74, p<0.05, Cohen's d = 0.38], and non-significant effects for Relational matrices and WM [$F_{(2,29)}$ = 0.004, p=0.99, and $F_{(2,29)}$ = 1.23, p=0.31, respectively]. Pairwise comparisons between stimulation conditions on Logic trials accuracy revealed no significant differences between tRNS and sham [$t_{(33)}$ = 1.78, p=0.253] or 40Hz-tACS [$t_{(33)}$ = 1.45, p=0.371].

Speed-Accuracy Tradeoff Analysis

We further examined whether the observed reduction of response times could be associated with a reduction of accuracy. Such a link could raise doubts about a potential modulation of speed-accuracy trade-off (SATO) (Pachella et al., 1974). Therefore, we assessed whether the correlation between stimulation-induced changes in both response times and accuracy was positive. This analysis revealed no significant correlations [r=0.19, p=0.294], consistent with the absence of a SATO in a previous study (Santarnecchi et al. 2013a).

Individual differences in efficacy of tES

We finally investigated whether improvement induced by 40Hz-tACS correlated with baseline performance. We therefore tested whether individual performance in the sham condition, which serves as our baseline performance, correlated with 40Hz-tACS induced reduction in time to solve Logic matrices in Experiments 1 and 2. Therefore, we collapsed the

data across Experiments 1 and 2 (N = 58). A significant correlation emerged between the time taken to correctly solve Logic matrices in the sham condition and the improvement in response times induced by 40Hz-tACS [Pearson correlation, $r_{(58)} = 0.75$, $p<0.01$](Fig.3). As a control analysis, and to rule out the possibility that the observed correlation was due to a regression to the mean effect, the correlation between response times during sham and 5Hz-tACS/tRNS induced reduction in response time was also tested. This analysis revealed no significant correlation [5Hz-tACS, $r_{(23)} = 0.18$, $p=0.435$; tRNS, $r_{(33)} = 0.28$, $p=0.225$] (Figure 3). Correlations for sham × 40Hz-tACS [$r_{(57)} = 0.51$, $p<0.05$] and sham × (sham - 40Hz-tACS) [$r_{(57)} = 0.75$, $p<0.01$] response times highlighted a significant interaction between baseline performance and the response to 40Hz-tACS. Notably, the correlation between 40Hz-tACS and individual performance in the sham stimulation condition was replicable in each experiment individually [Exp 1: $r_{(23)} = 0.46$, $p<0.05$; Exp 2: $r_{(18)} = 0.73$, $p<0.001$]. The enhancement obtained during 40Hz-tACS did not follow the distribution of the individual response times during the Sham condition, suggesting a difference between the two slopes (sham and 40Hz-tACS)(Fig. 3), and thus a nonlinear interaction between individual performance with and without stimulation. This hypothesis was confirmed through the application of Williams test to the two correlation coefficients ($Z = 3.72$, $p=0.007$). As a control for a regression to the mean phenomenon (Barnett, van der Pols, & Dobson 2005), the same analysis was applied for 5Hz-tACSand tRNS conditions, with no significant results.

Furthermore, a two-step clustering procedure, computed using performance at sham as the continuous discriminant variable, revealed two subgroups within the sample: *slow* and *fast* participants. *Slow* participants showed significantly greater improvement with 40Hz-tACS

compared to *fast* participants [Sham, $t_{(58)}$ = 4.2, p<0.001, Cohen's d = 1.68; 5Hz-tACS and tRNS, $t_{(58)}$ = 3.2, p<0.01, Cohen's *d* = 0.98] (Fig. 4A&B). Additionally, a differential responsiveness to 40Hz-tACS for these two subgroups was also identified [*slow*, $r_{(20)}$ = 0.85, p<0.001; *fast*, $r_{(33)}$ = 0.17, p=0.134], with 100% of slow participants benefiting from 40Hz-tACS, while 23% of *fast* participants exhibited impairments (Fig. 4C). In order to disentangle the possible influence of other individual difference variables on the baseline-dependent effect, further analyses also ruled out a significant impact of gender (Fig. S2, S2, S3), age (Fig. S4), order of stimulation blocks/cognitive tasks (Fig. S3) and baseline WM performance (Fig. S5) on the observed results.

Moreover, to exclude the possibility of experiments related differences in baseline performance, which might interact with individual response to tACS or tRNS and therefore bias the aforementioned baseline-dependent results, a comparison of baseline scores in both Logic, Relational and WM trials from Experiments 1 and 2 was carried out using a multivariate ANOVA. Results showed no significant differences in both RT [Logic, $F_{(1,55)}$ = 1.12, p=0.299; Relational, $F_{(1,55)}$ = 0.89, p=0.343; WM, $F_{(1,55)}$ = 0.93, p=0.332] and accuracy scores [Logic, $F_{(1,55)}$ = 0.67, p=0.413; Relational, $F_{(1,55)}$ = 0.84, p=0.381; WM, $F_{(1,55)}$ = 0.92, p=0.344].

Control task

Analyses of the odd/even task didn't reveal a significant main effects of the order in which blocks were presented on RT and accuracy in Experiment 1 [$F_{(3,81)}$ = 1.36, p=0.260, $F_{(3,81)}$ = 1.12, p=0.345, respectively] and Experiment 2 [$F_{(3,89)}$ = 2.01, p=0.118, $F_{(3,89)}$ = 0.62, p=0.60, respectively]. All pairwise comparisons were nonsignificant (p > 0.2). The same analyses were

also performed with blocks ordered by the stimulation type they followed (Figure S6), an important control that could have detected whether any of the stimulation types had general after-effects on RT or accuracy. Again, significant differences were not observed neither on RT or accuracy in Experiment 1 [RT: $F_{(3,92)}$ = 1.34, p=0.266, accuracy: $F_{(3,92)}$ = 1.02, p=0.375, respectively] and Experiment 2 [RT: $F_{(3,92)}$ = 1.65 p=0.187, accuracy: $F_{(3,92)}$ = 0.38, p=0.767, respectively]. As before, pairwise comparisons didn't reveal any significant comparison (p > 0.2).

Discussion

Here we show that the improvement in logical reasoning performance (i.e., reducing the time required to correctly solve a visuospatial fluid intelligence task) using prefrontal 40Hz-tACS can be predicted from baseline individual ability levels, with poorer performers exhibiting a greater benefit from 40Hz-tACS. Furthermore, we demonstrate that the effects on logical reasoning are frequency-specific, and are not due to a concurrent enhancement of spatial WM abilities or through a general change of brain dynamics leading to enhancement of cortical excitability due to tRNS.

Experiment 1 showed that the effect is specific to 40Hz-tACS in comparison to 5Hz-tACS. This was a clear-cut finding, despite using a “representative” frequency for gamma stimulation (i.e. 40Hz), rather than a more precise tACS frequency tuned on individual oscillatory peaks, which has been recently shown to induce greater modulatory effects on occipital alpha rhythm than not-individualized tACS (Vossen, Gross, & Thut 2015). Experiment

2 supported the efficacy of 40Hz-tACS in the enhancement of logical reasoning performance, but failed to show this effect with high-frequency tRNS (which instead led to trending lower performance than sham stimulation on accuracy). Therefore, these findings provide an insight about the functional relevance of γ-band activity in high-load G*f* tasks. Furthermore, the results indicate how the effect of 40Hz-tACS is related to the efficiency of the logical inferential process itself (indexed by the Logic trials), rather than nonspecific modulation of impulsivity-related network dynamics. The latter could lead instead to a generalized tendency to anticipate one's own responses in both correct and wrong trials, and, most importantly, to a generalized effect on all the trial types being tested (see Fig.2). Moreover, findings of Experiment 2 suggest that the effects of 40Hz-tACS are unlikely to be explained by an increase of cortical excitability, the putative neurophysiological effect of tRNS on brain activity (Terney, Chaieb, Moliadze, Antal, & Paulus 2008) (see Fig.2B). Although we did not directly measure cortical excitability induced by tRNS in this experimental context, this conclusion is in line with previous findings suggesting that 40Hz-tACS itself does not increase cortico-spinal excitability when applied on different neocortical regions: For example, the size of TMS-induced motor evoked potentials, indexing corticospinal excitability levels (Rossini et al. 2015), are not modulated by tACS at a range of different frequencies (including 30 and 45 Hz – flanking the frequency of stimulation in the present investigation) (Antal, Boros, Poreisz, Chaieb, Terney, and Paulus 2008;Feurra, Bianco, Santarnecchi, DelTesta, Rossi, and Rossi 2011;Feurra, Pasqualetti, Bianco, Santarnecchi, Rossi, and Rossi 2013); TMS-induced phosphene thresholds are decreased (i.e. cortical excitability is increased) by 20Hz but not 40Hz tACS (Kanai, Paulus, and Walsh 2010); 140 Hz tACS, but not 80Hz tACS, increases cortical excitability (Moliadze, Antal, and Paulus 2010). A more likely mechanism, which should be examined in future studies, is the entrainment of endogenous γ

oscillations, which could optimize local information processing, as evidenced from studies that used fast oscillations in the gamma band (Helfrich et al. 2014;Struber, Rach, Trautmann-Lengsfeld, Engel, and Herrmann 2014). Clearly, this hypothesis does not exclude possible additional network effects, with the modulation of local activity in the left MFG taking part to a rearrangement of interregional dynamics or just representing the result of a paradoxical improvement induced by the modulation of competitive opponent processes (Bestmann, de Berker, Bonaiuto 2015).

Animal work has demonstrated that tACS entrains neurons in widespread cortical areas (Ozen et al. 2010), with emerging experimental evidence that the effects of weak electric fields applied on optogenetically-controlled slices of pyramidal cells are constrained by their own endogenous cortical oscillations, according with the concept of state-dependency (Schmidt, Iyengar, Foulser, Boyle, and Frohlich 2014). Similar mechanisms may operate in humans, suggesting that tACS effects are critically dependent on the interactions with endogenous oscillatory activity, a mechanism which could explain the variability in the response to tACS as potentially due to the matching between the specific stimulation frequency applied and the correspondent individual spectral power of the brain oscillation being targeted (Kanai, Chaieb, Antal, Walsh, and Paulus 2008;Thut, Miniussi, and Gross 2012). Simulations, supported by empirical evidence, demonstrate that tACS modulates brain oscillatory activity via network resonance, suggesting weak stimulation at a resonant frequency could cause large-scale modulations of network activity (Ali, Sellers, and Frohlich 2013b). Importantly, the resonance frequency of a network could be modulated by the current task in which the network is being engaged. This would explain the task-dependent, frequency-specific effects observed with weak

electric fields in modeling studies (Schmidt, Iyengar, Foulser, Boyle & Frohlich 2014) and with tACS in humans (Feurra, Pasqualetti, Bianco, Santarnecchi, Rossi & Rossi 2013;Polania, Nitsche, Korman, Batsikadze & Paulus 2012;Santarnecchi et al. 2013a).

It is important to note that participants were relatively homogenous with respect to basal performance and age. At present, generalizing these findings to other populations, for instance different age groups or individual with initial or marked cognitive deficits, is premature. Research consistently suggests that these types of individual differences influence stimulation outcomes. For example, Tseng et al. (2012) showed that individuals with low visual short-term memory benefitted more from tES, while those with higher capacities did not show improvement. Similarly, Sarkar et al. (2014) showed that individuals with high mathematics anxiety benefitted from tES delivered while solving an arithmetic task, while the performance of low mathematics anxiety individuals was impaired. Along these lines, future work should be careful to extrapolate the present findings to other populations.

We can likely exclude that enhancement of visuospatial WM led to *Gf* enhancement, as we did not found effect of 40Hz-tACS on WM performance. However, considering the role of theta-oscillations in memory processing (Klimesch 1996;Polania, Nitsche, Korman, Batsikadze, and Paulus 2012), and the observed non-significant modulation of memory performance with 5Hz-tACS, it is also possible the WM task we adopted failed to capture this hypothesis, although it is a standard task for assessing visuospatial WM (Shallice 2003). The WM task also did not vary set size, and therefore may not have been sufficiently sensitive to capture changes in this limited-capacity store. Alternatively, it is also possible that tACS-induced WM enhancement

might need phase coupling of parieto-frontal oscillations (Polania, Nitsche, Korman, Batsikadze, & Paulus 2012), which was not tested in the current investigation.

One of the novel findings in this paper is that individuals performing slower at baseline benefit more from prefrontal 40-Hz stimulation. Even though this result can sound intuitive, the current evidence from other fields (e.g., education) shows that the effect can actually be the opposite. Namely, those with higher baseline abilities show greater improvement (Duncan et al., 2007). In our case, this kind of effect points out that tACS results could be due to individual differences at baseline, possibly reflecting individual frequency-specific differences like, in our case, reduced endogenous prefrontal gamma activity in slow responders. This hypothesis stems from the notion of increased task-evoked gamma activity in higher fluid intelligence individuals (Jausovec & Jausovec 2005) as well as the documented effect of gamma-based neurofeedback interventions on intelligence levels and feature binding (Keizer, Verschoor, Verment, and Hommel 2010). Given the high within-subject reliability inherent in the construct of fluid intelligence –as also confirmed by the low variability of our *Gf* estimates across conditions—the intriguing observation that tACS may depend on baseline performance could play an important role in future investigations on clinical populations where individualized neuromodulatory interventions might be crucial for success. Moreover, as recently suggested (Haier 2014;Jaeggi, Buschkuehl, Shah, and Jonides 2013), this finding also highlights the possibility that individual differences may be responsible for the heterogeneity in the outcomes of studies aimed at improving G*f* through WM training (Jaeggi, Buschkuehl, Shah, & Jonides 2014). Furthermore, while a baseline cortical excitability-dependent effect has been proposed in the context of WM modulation through transcranial direct current stimulation (tDCS)(Tseng et al. 2012), our

findings provide a frequency-specific evidence of such phenomenon, suggesting the individual difference in response to tACS as possibly dependent on pre-existing oscillatory patterns.These findings also have implications for brain responsiveness to external perturbation, which suggests that the magnitude of "instantaneous plasticity" achieved by reorganizing brain functions after, or during, stimulation could depend on the responsiveness of the system itself, which could be thought as a system "capacity" index (Krause, Marquez-Ruiz, & Cohen Kadosh 2013). From the perspective of human cognition and understanding of brain physiology, our findings suggest the existence of a somewhat general limit “imposed” by the interaction between cognitive enhancement and individual cognitive ability, which in the case of high-frequency oscillations apparently does not leave room for enhancement in those who already play at the top of the pyramid (see also Bonaiuto & Bestmann, in press).

Clearly, current results actively contribute to the mounting debate on both a critical analysis of tES induced “cognitive enhancement” and on the criteria for the application of the label "cognitive enhancement" or “neuroenhancement” itself. Here, we are using this label to refer to improving cognitive performance beyond the level performed by the individual, rather than expanding or augmenting the human capacity “beyond the species-typical level normal range of functioning” (Allen & Strand 2015). That being said, results as the one at hand might arise from very different combinations of physiological effects (Bestmann, de Berker, Bonaiuto 2015; Santarnecchi et al. 2015): even excluding the issue about the actual focality of tES interventions –which limits results interpretation per se— tES effects at the neural level might be mixed in nature and at the moment difficult from being considered a genuine enhancement of individual cognitive level. Indeed, increase in modulatory circuits actually triggering effects at

distance –e.g. inhibiting competitive networks— as well as worsening of other functions as a cost for the temporary increase in the skill being targeted (e.g., Iuculano & Cohen Kadosh, 2013; Sarkar, Dowker, & Cohen Kadosh, 2014), are just two scenarios which might underpin focal, selective cognitive improvements like the one observed in the present investigation.

Therefore, looking at a possible translational perspective of tES, studies inquiring both local and far transfer of effects by assessing a variety of cognitive functions are needed (i.e. beyond WM, the cognitive domain which remained unaltered in the current investigation), together with electrophysiological/imaging data to further increase our understanding of tES effects at neural levels.

Nonetheless, noninvasive brain stimulation using tACS, if properly tuned with endogenous oscillatory brain activity, may help to reduce interindividual differences in cognitive abilities due to innate, acquired or developmental origins (Cohen Kadosh et al., 2014). Additionally, future studies should examine whether this approach will necessarily benefit from a more precise individualization of the applied frequency of stimulation according with a sub-band tuning rather than using an average frequency of stimulation, as suggested by modeling investigations (Schmidt, Iyengar, Foulser, Boyle, & Frohlich 2014). In this view, the lack of individualization of tACS might ultimately even led to an underestimation of positive effects of 40Hz-tACS on individual logical abilities.

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Figures captions

Fig. 1. Graphical representation of the experimental setup. (A) An example of Relational and

Logic trials from the Sandia matrices, and of the delayed-match-to-sample change-localization working memory (WM) task. (B) A schematic representation of the experimental design. Trials were randomly presented in order to avoid carry-over effects (red and blue boxes don't represent the actual randomization order). The order of stimulation was counterbalanced across participants using a Latin Square design. (C) tES setup adopted in both experiments. Electrodes were positioned according to the 10-20 International EEG System: the active electrode was centered on left middle frontal gyrus [MNI coordinates: x = -34, y = 16, z = 30], whereas the return electrode was placed on Cz (vertex).

Fig.2. Effect of 40Hz-tACS on G*f* performance in both experiments. Significant reduction in response latencies to correctly solve Logic matrices during 40Hz-tACS condition in Experiment 1 (A) [40Hz-tACS vs sham, $t_{(23)}$ = 5.84, p<0.001, ~21% reduction; 40Hz-tACS vs 5Hz-tACS, $t_{(23)}$ = 3.57, p<0.01], and Experiment 2 (B) [40Hz-tACS vssham, $t_{(23)}$ = 2.40, p<0.021, ~13%; 40Hz-tACS vstRNS, $t_{(23)}$ = 2.89, p<0.01]. No significant effects for Relational trials were observed (C-D). Response time scale is in seconds. Error bars are ± one standard error of mean.

Fig.3. Baseline-dependent effect of 40Hz-tACS. (A-B) Correlation scatterplots for baseline performance (Sham) × 40Hz-tACS and enhancement with 40Hz-tACS (defined as Sham - [40Hz-tACS]), response times (i.e., the time required to correctly solve each matrix), respectively. Data from sham and 40Hz-tACS have been collapsed between the two experiments

(n=58). These results highlight a significant interaction between baseline performance and the response to tACS. (C) No significant correlations between sham and 5Hz-tACS or high-frequencytRNS (101-640Hz), thus excluding a regression to the mean effect. Response time scale is in seconds.

Fig.4. Cognitive enhancement as a function of individual differences. (A) Separation between slow and fast responders at baseline. As shown in the boxes, fast (red) and slow (blue) participants did not differed for age or enhancement by 5Hz-tACS, while they clearly shown a differential response to 40Hz-tACS. (B) Different response to 40Hz-tACS specifically observed in slow responders. (C) Differential response rate to 40Hz-tACS for these two subgroups, with 100% of slow participants showing a benefit from tES, while 23% of *fast* participants exhibited a deterioration in their performance. Response time scale is in seconds. Error bars are ± one standard error of the mean.

Individual Differences and Specificity of Prefrontal Gamma Frequency-tACS on Fluid Intelligence Capabilities

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Supplemental Figures Legends

S1. Accuracy levels in Logic and Relations matrices. Figure reports accuracy and response times for both Experiments (Experiment 1, A; Experiment 2, B). Error bars are ± one standard error of the mean (SEM).

S2. Results of working memory task. Analysis of performance during Delayed-Match-to-Sample task revealed no effect for both tACS (A) and tRNS (B) on Accuracy and RT. Results are also shown for male and female participants. Response time scale is in seconds. Error bars are ± one SEM.

S3. Effect of tACS conditions and tasks order. Average values for the enhancement with 40Hz-tACS are provided for the overall dataset (n=58), grouped by WM/Gf tasks (A) and stimulation type order (B). Additional averages for male and female participants are also displayed in the lower panels. No differences for tACS/tRNS conditions order and priming effects for preceding cognitive tasks were observed. G, S and T respectively stand for Gamma, Sham and 5Hz/tRNS stimulation conditions.

S4. Effect of Age on response times. No significant correlations between age and response times during 40Hz-tACS (upper row) and the observed speedup captured by Sham minus 40Hz-tACS (lower row) were found. Response time scale is in seconds.

S5. Correlation between WM and Logical reasoning. Panel A shows the correlation between response times for the WM task during Sham stimulation and those for logical matrices during 40Hz-tACS. Assuming WM performance at baseline as a mediator of logical reasoning and thus a predictor of response to 40Hz-tACS, significant correlations would be expected. Our data does not support such hypothesis in both studies (see R values, all p values > 0.05). Furthermore panel B shows the principal component analysis (PCA, Varimax rotation) on Experiment 1 and 2 datasets, revealing a clear separation between WM and G*f* components. Response time scale is in seconds.

S6. Results of control task. Subjects were asked to categorize as odd or even 100 randomly generated numbers, with the purpose of allowing a disengagement from the main task while monitoring -through reaction times- potential effects of reduced attention and fatigue throughout the experiment. Panel A and B report accuracy (upper row) and reaction time (lower row) for study 1 and 2, showing a steadily high level of accuracy through the entire experiment (Experiment 1: mean ACC=0.92; Experiment 2: mean ACC=0.87) consistently through all participants. Baseline refers to the first time the task was presented, i.e. preceding the first main experimental block. The data are plotted according to the stimulation type they followed ("post-stim"). Analysis revealed no significant differences between any of the RTs or accuracy following a stimulation type in either Experiment 1 or 2. Response time scale is in seconds. Error bars are ± one SEM.