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GRAPHEME-COLOR SYNESTHESIA INDUCTION WITH V4 TRANSCRANIAL DIRECT CURRENT STIMULATION

Grapheme-color synesthesia (GC-S) is a neurological condition in which the perception of a grapheme elicits the experience of color or even the visual representation of that grapheme as colored. Previous research using transcranial magnetic stimulation on GC-synesthetes demonstrated enhanced excitability of the visual cortex. Consequently, we hypothesized that using anodal "offline" transcranial direct current stimulation on the visual cortex in area V4 followed by visual training could boost cortical excitability in the target areas and thus produce effects similar to GC-S in non-synesthetes. We discovered that after anodal stimulation, participants had a considerably smaller mean change in reaction time on white symbols than after sham and cathodal stimulation. Our findings indirectly support the cross-activation hypothesis.

JEL Classification: Z39.

Keywords: tDCS, Grapheme-color synesthesia, Cross-activation, Visual cortex.

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Introduction

Synesthesia is a perceptual phenomenon in which stimulation of one sensory or cognitive pathway elicits involuntary experiences in another sensory or cognitive pathway [1*]*. There are two types of synesthesia: the projection type and the association type. The first manifests as real sensations and feelings superimposed on the object. The second is expressed as intuitive knowledge or impressions that are not perceived by the individual experiencing them. However, this distinction is somewhat arbitrary, yet accepted by most researchers of synesthesia, since the synesthete can perceive sensations "in the middle". According to studies, the associative form is present in 89% of cases [2]. Most synesthetes begin to experience this phenomenon in early childhood. Regarding grapheme-colour synesthetes, most perceive the same colours for the same stimuli, meaning that the colour perceived in response to a particular grapheme is stable and persists over years [3].

It has been observed that the colouring areas are located in V4 [4,5,6]. Furthermore, the grapheme perception area is located in the fusiform gyrus [7] which is very close to V4. Brang [8] showed increased activity of V4 in synesthetes. This suggests the areas associated with the most common form of synesthesia, the perception of graphemes and the perception of colours, are located near each other. Thus, the cross-activation hypothesis [9] proposes that there is a cross-connection between these two regions resulting in this type of sensation.

Recent studies suggest that grapheme-colour synesthetes had significantly higher activation and anisotropy in the inferior temporal cortex than non-synesthetes [10]. It was discovered that synesthetes-associators and synesthetes-projectors have different activation, but all synesthetes have activation between V4 and the fusiform gyrus [11]. Specifically, projector synesthetes showed an activation that was consistent with an immediate cross-activation of V4 via the bottom-up fusiform pathway. Additionally, associator synesthetes showed activity that was more consistent with top-down feedback from the parietal lobe. This difference in dynamic interaction between projectors and associators is only in the dynamics; the localisation and the main mechanism are the same. Activation is a crucial and irrefutable evidence for the cross-activation hypothesis [12].

By applying repetitive transcranial magnetic stimulation (rTMS) to the visual and motor cortex of synesthetes, Terhune [13] recorded phosphene and motor thresholds. According to this study, synesthetes had phosphene thresholds (a specific visual sensation that occurs in the absence of light on the visual organ) that were approximately 300% lower than those of the control group, when compared to motor thresholds. Their findings suggested grapheme-color synesthesia involves enhanced excitability of the visual cortex, and that the modulation of cortical excitability is related to the perceived vividness of the synesthetic color. In this way, transcranial direct current

stimulation (tDCS) and other forms of transcranial electrical stimulation could be used as a tool to modulate changes in the activity of the visual cortex, with corresponding changes in visual perception and behaviour. Our hypothesis is that the effects of tDCS could induce grapheme-like colour synesthesia in non-synesthetes. We therefore suggested that anodal offline tDCS over visual cortex in V4, followed by visual training, could modulate cortical excitability in the target areas, producing effects similar to grapheme-colour synesthesia in non-synesthetes.

Methods

Participants

All participants provided a written informed consent. The ethical approval for this study was given by National Research University Higher School of Economics Committee on Interuniversity Surveys and Ethical Assessment of Empirical Research in accordance with the Declaration of Helsinki. All experiments in this study were performed in accordance with current guidelines on transcranial electrical stimulation in humans. The participants had normal or corrected-to-normal vision, no metallic implants or electrical devices, no history of substance abuse, migraines, or neurological or psychiatric disorders, and were not taking any medication. The mean age was 21.8 years, with a standard deviation of 1.5 years. Twenty-nine percent of respondents had completed higher education, while the remaining 71 percent had incomplete higher education. Seventeen percent were male and 83 percent were female. In total, 71 respondents participated in the experiment. The anodal group consisted of 25 participants, the cathodal group of 22, and the sham group of 24. Subsequently, five people were removed from the experiment, one from the anodal group and four from the sham group, as they had an error rate greater than 50% compared to the other test subjects. The stimulation was randomized among the respondents and the results of the experiment were anonymized.

Experimental paradigm

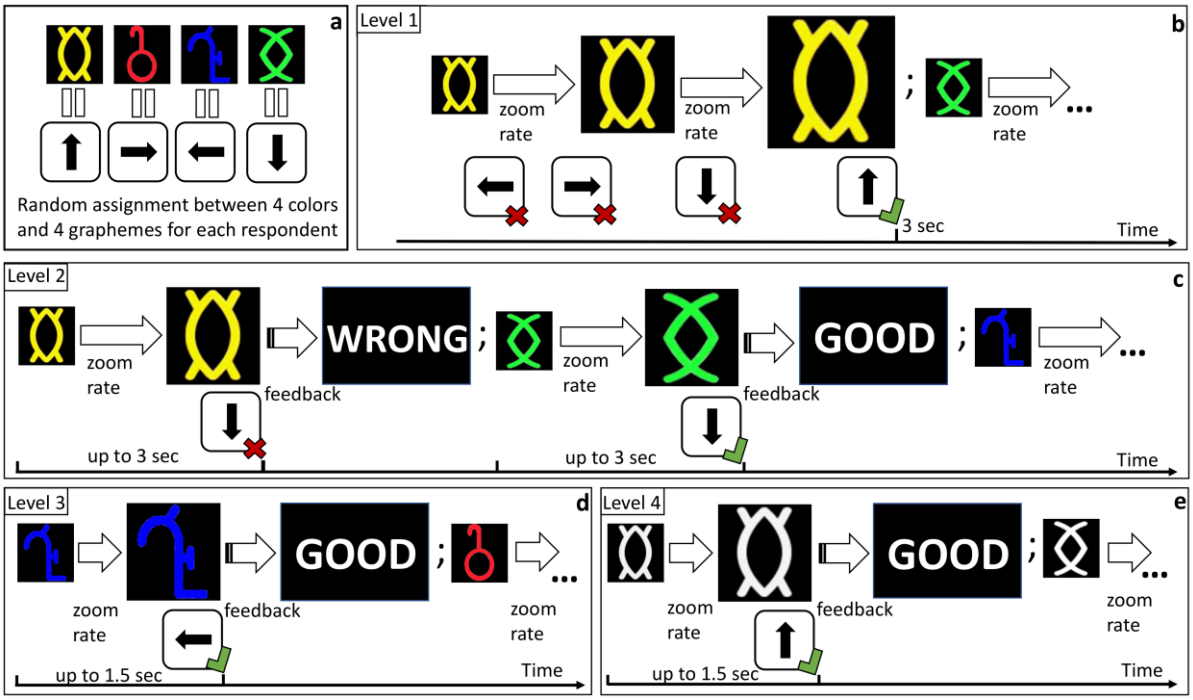

Fig 1. Experimental design. A. The buttons (arrows on the keyboard) corresponding to each symbol were randomized for each respondent, the sequence of symbols on the screen was also randomized, no more than 3 identical symbols in a row were allowed. The colors of each symbol

The experimental design, as shown at Figure 1, was based on speeded congruency test [20] and allowed us to investigate the presence of synesthesia-like sensations in non-syntesthetes. In total, the game consisted of four rounds, with 100 repetitions per round. During the first (training) phase, a colored symbol appeared on the screen and started to gradually increase in size. The purpose of this phase was to train the subject's memory as to which button corresponded to which symbol. If the subject responded incorrectly, the symbol would increase further and would only be replaced with the next symbol after the correct button had been pressed.

In the second round, or round of normalization, colored symbols were presented on the screen and increased in size until the subject pressed one of the buttons. If the response was incorrect, a "WRONG" message was displayed; if it was correct, a "GOOD" message was shown. The stimuli presented in this round were used to compare the results of the subsequent rounds with this one and to normalize the results.

The third round was the first round of difference testing, which was identical to the previous one, except for the speed of the increase in letters. The purpose of this step was to compare the response time to rapidly changing symbols between the experimental group and the control group.

According to our hypothesis, the participants who received an active stimulation would respond faster.

The fourth round was the final round for testing differences. In this round, the stimuli were presented at the same speed as in the third round, but they did not have any color (i.e. the symbols were white). The purpose of this round was to compare the reaction time in response to colorless symbols.

The rules of the game were to press the corresponding button quickly and accurately. To prevent any experimental biases, we randomized each time the connection between buttons and symbols as well as colors and symbols. Moreover, we limited the number of repeated symbols in the sequence to no more than three. Every symbol appeared on the screen and increased until the button was pressed or the time run out. Each level consisted of 100 repetitions of this procedure. In every level, except the training level, a message of "WRONG" was displayed when the answer was incorrect and "GOOD" when the answer was correct.

Experimental procedure

At the beginning of the experiments the participants were asked to sign an informed written consent and complete a questionnaire with socio-demographic information. The participants were then randomized into experimental and control groups. The experimental group first underwent a stimulation session, as described below. The control group, however, received no stimulation, yet were led to believe that they were being stimulated. To prevent any bias, a stimulation device and a cap with electrodes were placed, and a weak direct current was delivered, making the stimulation perceivable but not enhancing neural activity. After the stimulation, the experimenter, who was unaware of the participants' group assignment, provided instructions about the game. At the end, the participants were debriefed.

We used Presentation software (https://www.neurobs.com/) for the presentation of the stimuli and recording the subjects' responses. An experimental paradigm was constructed in NBS Presentation Software. The data was analyzed in Statistica 12 Software Package. Algorithms for log parsing and reaction time normalization were encoded using Python 3.

TDCS

A Transcranial Electrical Stimulation System with EEG Recording Capability (8 Channels) Starstim (Barcelona, Spain) was used for the stimulation. The stimulation protocol was programmed using the NIC2 Software. The modelling of the electrical stimulation protocol was performed using SimNIBS Software [21].

Using the NIC2 software, we prepared three stimulation protocols corresponding to three groups based on the reviewed scientific literature: anodal stimulation, with two anodes placed bilaterally over the target areas; cathodal stimulation, with two cathodes placed bilaterally over the target areas; and placebo (sham) stimulation, when an electric current was delivered only for the first and last 10 seconds of stimulation. This procedure allows the respondent to feel a specific itching or mild tingling sensation at the electrode locations, but does not cause any significant neurophysiological effects. The stimulation time in this case is 10 minutes and 10 seconds (including five seconds for the rise and five seconds for the fall of the electric current). Based on stimulation studies, an optimal and safe current level of 1.5 mA was determined. Physiological saline solution (NaCl 0.9%) was used as an electrolyte. We used four electrodes for each stimulation protocol, each consisting of a sponge cap, a carbon rubber core, and a nickel-plated brass metal pin: two pieces with a contact surface of 8 cm2 and two pieces with a contact surface of 25 cm2.

Based on previous research [22], we developed the following setup for all three groups: target electrodes of 8 cm2 were placed at P09 and P010 according to the classic EEG scheme (10-20). This size was chosen in order to increase the current density in this region. As a reference, we used FC3 and FC4, where electrodes of 25 cm2 were placed to decrease the current density. This was done to reduce the impact on the sensorimotor cortex located in this area and to reduce the likelihood of adverse variables associated with the stimulation of these areas. Thus, our setup can be characterized as bi-anodal (in that we have two target electrodes (anodes) and two reference electrodes) and bilateral (in that both hemispheres are stimulated) for anodal stimulation. In terms of waveform, our stimulation is monophasic, meaning that the current flowed continuously in one direction throughout the stimulation.

Results

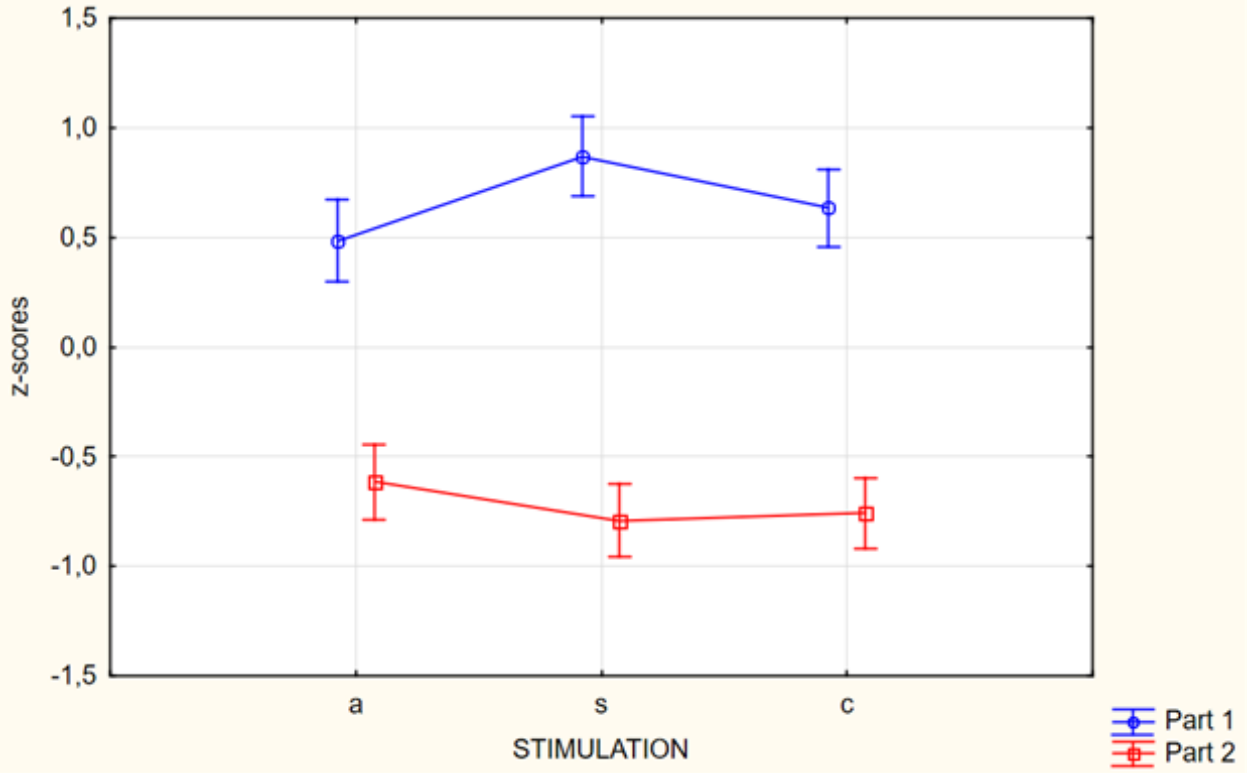

Fig 2. Mean normalized reaction time (RT). RT is shown in response to colored and colorless stimuli across levels. A - anodal, S - sham, C - cathodal group.

For each subject, two metrics were calculated. First, the z-colored score (hereinafter referred to as z_c), which is the mean reaction time on the second level minus the mean reaction time on the first level divided by the standard deviation of the first-level reaction time. The same method was used to calculate the z-white (hereinafter referred to as z_w), which is the mean reaction time on the third level minus the mean reaction time on the first level divided by the standard deviation of the first-level reaction time. We introduced those metrics to obtain normalized results that are designed to avoid experimental biases.

For the obtained data, we used a mixed model ANOVA for the per-participant mean z-scores in STATISTICA 12 software package. We determined two factors, Stimulation (anodal, cathodal and sham) and Part (Part 1 equal to testing colorless symbols and Part 2 equal to testing colored symbols).

The mixed-model ANOVA revealed a significant effect of Factor Part ($F(1, 60) = 377.37$, $p < 0.0001$, $\eta p2 = 0.86$) and an interaction between the two Factors, Part × Stimulation ($F(2, 60) = 5.0356$, $p = 0.00951$, $\eta p2 = 0.14$). The Bonferroni-corrected post hoc analysis highlighted the

difference in performance between the anodal and sham groups in Part 2. Figure 2 shows that the reaction time in the anodal group was faster than in the sham group.

Discussion

Using noninvasive brain stimulation techniques, we show that anodal tDCS applied to V4 could induce a sensation similar to grapheme-color synesthesia in non-synesthetes. Our study revealed that the subjects demonstrated a significantly shorter average reaction time to white symbols after anodal stimulation compared to the control group (sham stimulation), and to the cathodal group. Furthermore, no statistical differences in performance were observed between the other groups. After the stimulation, one subject reported vivid synesthetic experiences. In a one-on-one interview a few days after the experiment, this person reported experiencing color-related sensations when hearing names and upon visual observation of family members for one hour following stimulation. Several people in the cathodal group reported visual sensations such as dark and light stripes superimposed on the main background between three and eight minutes after the stimulation. This suggests our results are in line with the cross-activation hypothesis and that the anodal stimulation causes a sensation similar to synesthesia for a short period.

There are limited studies that also provide evidence for the cross-activation hypothesis. Amsel [12] demonstrated cross-activation of V4 via the ascending pathway in the fusiform gyrus in synesthetes when presented with graphemes. Recent studies also reported an induction of synesthesia in non-synesthetes [14, 15, 16, 17]. However, these studies had numerous limitations that could be critical for understanding the phenomena and analyzing the results, such as post-hypnotic suggestion, application of LSD, visual deprivation [14,17, 18, 19]. Moreover, all of these studies that induced synesthesia only tested its manifestation by introspection or using a questionnaire, which severely limits an interpretation of the obtained results. While it has been shown that synesthesia involves the cross-activation of different sensory modalities, it is not clear how previous sensory experience may influence the development and expression of synesthesia. For example, it is not clear whether individuals with synesthesia have experienced more cross-modal associations in their past, or whether their synesthetic experiences are purely innate. Future studies might shed a light on the cognitive mechanisms that underlie synesthesia, including how synesthetic experiences may affect higher-level cognitive functions.

Taken together, these findings indicate that the V4 region plays a role in the perception of grapheme-color associations in non-synesthetes, which was successfully confirmed in our study with non-invasive brain stimulation, allowing to establish a causal link. We speculate that anodal tDCS to V4 increase baseline cortical excitability and hence attenuates the sensory experience by

modulating the signal-to-noise ratio underlying the experience of synesthesia-like sensations in non-synesthetes.

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