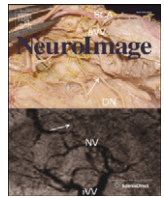




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TDCS guided using fMRI significantly accelerates learning to identify concealed objects

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ABSTRACT

The accurate identification of obscured and concealed objects in complex environments was an important skill required for survival during human evolution, and is required today for many forms of expertise. Here we used transcranial direct current stimulation (tDCS) guided using neuroimaging to increase learning rate in a novel, minimally guided discovery-learning paradigm. Ninety-six subjects identified threat-related objects concealed in naturalistic virtual surroundings used in real-world training. A variety of brain networks were found using functional magnetic resonance imaging (fMRI) data collected at different stages of learning, with two of these networks focused in right inferior frontal and right parietal cortex. Anodal 2.0 mA tDCS performed for 30 min over these regions in a series of single-blind, randomized studies resulted in significant improvements in learning and performance compared with 0.1 mA tDCS. This difference in performance increased to a factor of two after a one-hour delay. A dose-response effect of current strength on learning was also found. Taken together, these brain imaging and stimulation studies suggest that right frontal and parietal cortex are involved in learning to identify concealed objects in naturalistic surroundings. Furthermore, they suggest that the application of anodal tDCS over these regions can greatly increase learning, resulting in one of the largest effects on learning yet reported. The methods developed here may be useful to decrease the time required to attain expertise in a variety of settings.

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Introduction

Background

Theoretical accounts (Chase and Simon, 1973; Ericsson and Staszewski, 1989; Ericsson et al., 2006) and reports of well-known experts (Gladwell, 2008) typically propose that expertise develops only after an extensive length of deliberate practice. It would be of both theoretical and practical interest if methods were developed that shorten the training required to develop expertise. Expertise includes a collection of learned skills needed to accomplish a set of tasks. One such skill required for many everyday and work settings is the identification of obscured and concealed objects in a complex environment. Examples include radiologists examining X-ray or MRI

images for tumors, oceanographers scanning satellite imagery for ocean circulation patterns, pilots navigating in bad weather and operators examining surveillance videos for specific objects or people, among many others. Understanding the neural basis of how people learn to perform such tasks would help considerably in designing aids to boost performance and to develop better training techniques in work settings, consistent with the neuroergonomics approach (Parasuraman and Rizzo, 2008; Parasuraman and Wilson, 2008). These could lead to neuroscience-based techniques that would increase the effectiveness of training and reduce the time required to achieve a required level of expertise.

One such technique that might benefit training is transcranial direct current stimulation (tDCS). TDCS uses very small electric currents applied to the scalp, and is considered to be safe for experimental use in healthy subjects (Bikson et al., 2009). The precise mechanisms by which tDCS influences behavior are uncertain, but may involve altering the electrical environment of cortical neurons, causing separation of charges within dendrites and cell bodies, leading to small changes in membrane potential (Bikson et al., 2006). NMDA receptor-dependency

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of the after-effects of tDCS have also been observed (Liebetanz et al., 2002), which suggests that tDCS may interact with glutamatergic systems found to be important for learning (Bliss and Collingridge, 1993).

Study goals

The present study had three principle goals: (1) to determine which brain regions are involved in identifying disguised and concealed objects placed in naturalistic surroundings; (2) to examine changes in brain networks associated with learning to recognize these objects; and (3) to use brain stimulation to verify and extend these imaging findings and to increase learning rate for this task. We hypothesized that stimulation of brain networks involved in perception and learning would lead to faster learning and improved performance. In order to identify the brain networks most likely to facilitate learning, we developed a novel discovery-learning task in which subjects learned to identify concealed threats in a virtual naturalistic environment. This task was used with neuroimaging to identify networks involved in perception and learning, and these data were used to select those networks that were most accessible to brain stimulation using tDCS. To our knowledge, no prior published studies have examined the effects of brain stimulation on learning to identify complex visual stimuli of the type found in natural scenes. The neural effects of tDCS are influenced by parameters of stimulation that affect the path of electric current through the brain and the current strength at specific brain locations (Nitsche et al., 2007). Hence, we hypothesized that the effect of tDCS on learning should be sensitive to current strength and electrode location, which was varied across studies.

Materials and methods

Subjects

A total of 104 healthy subjects provided informed consent to take part in these studies, which was approved by the University of New Mexico Health Sciences Center Institutional Review Board. Of these, six subjects were consented as a part of these studies who were later rejected for unusual levels of performance. These six included subjects whose performance was more than two SD above or below the mean level of performance (three subjects more than 2 SD above and three below). Another two subjects reported sensations of burning or pain during tDCS, one receiving full-current and one low-current tDCS. After removing these eight, data from 96 subjects remained for analysis.

Prior to enrollment in the study, subjects were screened and excluded for having a primary language other than English, history of head injuries or concussions, left-handedness (Oldfield, 1971), current or previous history of mental, neurological, alcohol or drug abuse disorders, current prescription medication affecting CNS function, or uncorrected hearing or visual impairments. In addition, subjects who participated in the imaging studies were excluded for metal implants, claustrophobia and pregnancy, and subjects who were given tDCS were rejected for metal head implants and for sensitivity to latex.

Concealed object learning paradigm

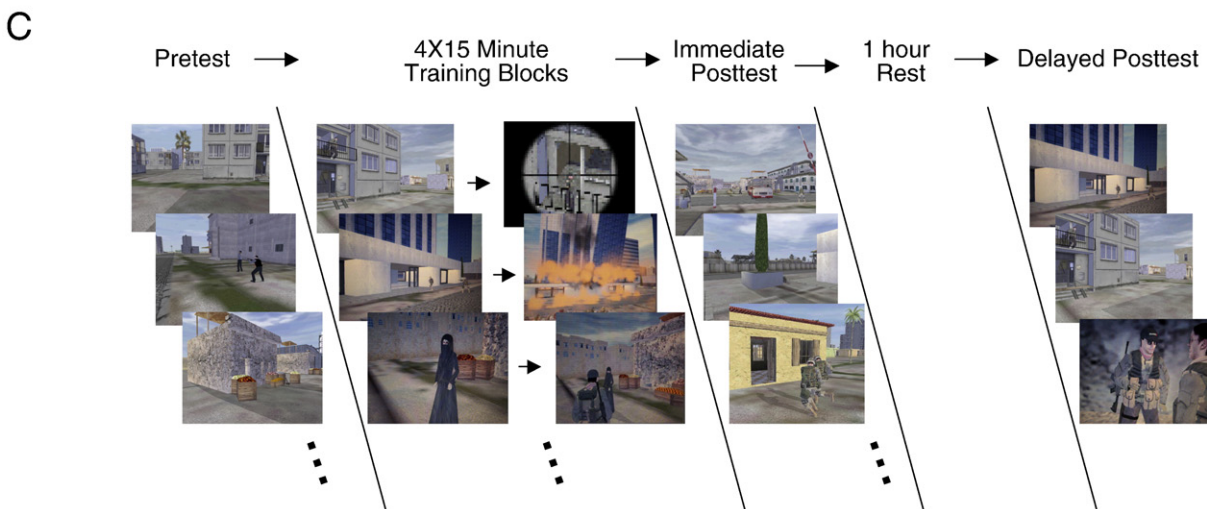
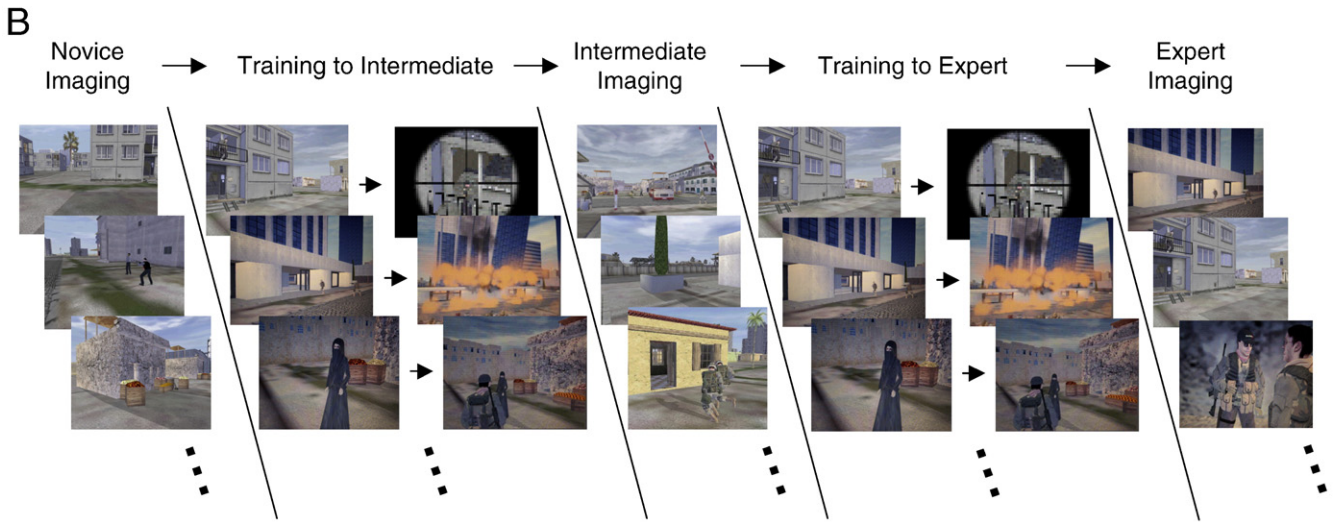
In order to study the brain basis of disguised and concealed object detection, a concealed object-learning task was developed, based on the “DARWARS Ambush!” virtual reality environment (MacMillan et al., 2005; Raybourn, 2009), which is used to familiarize military personnel with the middle-eastern environment before deployment (Fig. 1). This environment provided naturalistic stimuli and offered sufficient flexibility to provide a variety of different contexts and cues for concealed objects of varying detection difficulty for use in this study.

Individual scenes were captured as short movies for presentation within the learning task. Still images were extracted from the movies and approximately half were manipulated to include specific concealed objects. Concealed objects included bombs that were concealed by, or disguised as, deceased animals, roadside trash, fruit or other objects such as oil barrels, boxes, cars, toys and other items. Enemy combatants could take the form of snipers in various concealed locations, plainly clothed suicide bombers, and others. In each case, similar scenes without disguised or concealed objects were created that differed by one or more discernable characteristics. Objects and features that indicated the presence of concealed objects were selected that were ambiguous on first viewing but could be identified after training, as determined by a series of initial pilot studies.

A discovery-learning paradigm was used (Bruner, 1961). Discovery learning is a naturalistic form of training, which involves subjects learning with minimal guidance, based on their ability to gain knowledge from experiences gained during interactions with the environment, in this case by interacting with the experimental paradigm. Before training, subjects were instructed that they would be in charge of a mission that is taking place in a middle-eastern country. No details were given as to the precise nature of possible threats or the cues that could be used to predict their occurrence. These were discovered over the course of training. During training, still images were presented for 2 s each, followed by 1 s of a blank screen with a crosshair (Fig. 1). Subjects were required to make a button press response within 3 s after stimulus onset indicating if they detected a disguised or concealed object that indicated a potential threat, or no such object was detected. A short feedback movie was then presented. Four outcomes were possible: if a concealed object was present in the image but was missed by the subject, the feedback movie showed the outcome, e.g., a sniper attack or bomb blast occurring, which the subject could use to infer the nature of the missed object and then detect the same or similar object on subsequent trials. At the same time, computer-generated voice-over indicated that the object had been missed and there had been a casualty, but gave no specific information as to the identity of the object. If a concealed object was present and detected, the movie showed the scene progressing without harm and the voice-over complimented the subject for their performance. If a concealed object was not present, and the subject incorrectly indicated that it was present, the voice-over chastised the subject for delaying the mission. Finally, when there was no concealed object and the subject indicated this correctly, the voice-over praised the subject. Training trials each lasted an average of 12 s. Blocks of 60 trials lasting 12 min each were administered, with short rest periods between, for an average of 15 min total per block.

For testing before and after training, still images were presented without feedback movies. Stimuli were presented for 2 s, with jittered

Fig. 1. Shows examples of stimuli used for fMRI and tDCS learning studies. A. Shows examples of stimuli with and without concealed objects. Of the six example scenes, four contain hidden objects, while the other two do not. Of the four with hidden objects, two contain hidden enemy soldiers, and two contain hidden bombs. Difficulty of object detection was adjusted by modifying the size and distinctiveness of objects. B. Illustrates fMRI learning study paradigm performed in 13 subjects. Each subject was first scanned using fMRI at the novice stage using 100 static scenes without feedback. After imaging, subjects performed up to 90 min of training per day. Each training trial was composed of a static scene, to which subjects responded if they observed a concealed object or not, which was followed by a short feedback movie. After subjects achieved 78% accuracy, they were imaged again at the intermediate level. Training was continued for seven of these subjects until they achieved 95% accuracy, and were imaged a final time at the expert level. C. Illustrates paradigm used for behavioral tDCS learning studies. Each session began with a pretest using static scenes without feedback. This was followed by four training runs, with 60 training trials per run. Subjects received tDCS for 30 min, beginning 5 min before training was started, then additional training without tDCS, for a total of 1 h of training. After training, an immediate posttest was obtained, followed by a one hour break, and a delayed posttest.



4–8 second inter-trial intervals using a crosshair placed on a gray background. As with training, subjects were asked to indicate if a concealed object was present in each image within 3 s after stimulus onset. Each test block included 50 stimuli, lasting a total of 5 min. Six test blocks each were used for the novice, intermediate and expert fMRI imaging studies, and two test blocks each for the pre-test, immediate posttest and delayed posttest in tDCS behavioral learning studies 2–4.

Imaging studies of concealed object learning

To identify the brain networks supporting the identification of concealed objects and changes with learning, we performed an fMRI study in 13 subjects (mean age 22.3 years, SE 0.3, mean years of education 15.0, SE 0.5, 6 female). Subjects performed the object recognition task without feedback while undergoing fMRI. The fMRI imaging data were then analyzed using SPM, and also using our recently developed non-linear discrete dynamic Bayesian network analysis (DBN; Burge et al., 2009).

After the initial novice imaging session, subjects underwent training sessions with feedback outside of the scanner. Separate 1.5 hour training sessions were repeated on sequential days until the subject reached an intermediate level of performance, determined to be greater than 78% correct responses on two consecutive training blocks. This level of accuracy was chosen as it fell just above the midway point between chance performance (50% in this two-choice paradigm) and perfect accuracy (100%). Following training to the intermediate level, the 13 subjects each completed a second fMRI session using the same method and procedure as the novice-level scan. Seven of these subjects were then trained in additional training sessions until reaching expert level performance (>95% correct responses), as no subjects were able to achieve perfect accuracy in a reasonable length of training time. A final neuroimaging session was then completed in these seven subjects following the same method and procedure used in the prior fMRI sessions. Subjects were asked to complete a screening questionnaire before each imaging session.

All fMRI data collection was performed using a Siemens TIM Trio 3 Tesla MRI system. Images were presented with a JVC DLA Multimedia projector (Model DLA-SX200-NLG) using Presentation Version 11.1.0. Thirty-two axial slices (3.5 mm thick) were collected using a gradient-echo echo-planar pulse sequence (repetition time: 2,000 ms; echo time: 29 ms; field of view: 240 mm; flip angle: 75°). High-resolution T1-weighted scans were acquired for anatomical localization of hemodynamic response. All preprocessing and GLM-based statistical analyses of data were carried out using SPM and AFNI. The locations of significant peak foci were obtained using the Talairach coordinate system.

Dynamic Bayesian network (DBN) analysis

DBN was used to identify brain networks involved for two reasons. Firstly, fMRI typically reveals that many regions are involved in a particular cognitive task, without specifying the most critical areas. We used DBN to identify the specific cortical networks involved in performance of our object recognition tasks, and changes in these networks were examined across stages of learning. Secondly, DBN uses Bayesian statistics that reveals both linear and non-linear associations among brain regions, and is thus potentially more sensitive to associations that might be missed by linear methods, as described in Burge et al. (2009).

Models of expertise-dependent activity networks were extracted from the fMRI data via DBN structure search algorithms (Burge et al., 2009; Koller and Friedman, 2009). The imaging data were parcellated according to the AAL atlas in MNI space (Tzourio-Mazoyer et al., 2002). Separate DBNs were identified for the novice- and intermediate-level subject pools using the approximate conditional likelihood

(ACL) objective function, which identifies the networks that maximally discriminate the novice and intermediate training stages. Confidence tests were applied to sub-networks associated with each ROI using a Z test under null distribution generated by bootstrap resampling with $p < 0.05$ (Prichard and Theiler, 1994). Networks that passed the confidence threshold were further filtered for repeatability under cross-validated holdouts of the subject populations.

tDCS learning studies of concealed object detection

An Iomed Phoresor PM850 was used to administer tDCS current. Square-shaped, 11 cm², water-soaked sponge electrodes, held by a rubber casing, were applied to the scalp using elastic bandage material. The anode was placed on the scalp over the target location and the cathode was placed on the contralateral upper arm. Subjects were kept blind to a manipulation of current strength in the study.

Subjects received tDCS for a total of 30 min, during training blocks one and two, beginning 5 min before training was started. During application of tDCS, subjects were asked to describe physical sensations using a list of 10 descriptors, numbered as: 0) no sensation, 1) cold, 2) some tingling, 3) warm, 4) lots of tingling/some itching, 5) very warm, 6) lots of itching, 7) burning (like a sunburn), 8) burning (like scalding water) and 9) "hurts a lot". The administration of tDCS was stopped immediately if subjects reported 7 or above. After tDCS administration was complete, the electrodes were removed, and the third and fourth training blocks were performed. Subjects were also asked to complete a mood assessment before and after each training session. No significant changes in self-reported mood were found between groups receiving different levels of current. This phase of the study is composed of four separate experiments, and the details of which are described in turn.

For Experiment 1, the anode was placed over right inferior frontal cortex, centered nearby to electrode site F10 over the right sphenoid bone in 27 subjects. Thirteen subjects received full-current tDCS and 14 received low-current tDCS. In order to verify and extend the findings of Experiment 1, Experiment 2 was performed in 36 additional subjects using the same training methods. Thirteen received full-current tDCS and 23 received low-current tDCS. A larger number of low-current subjects were acquired in order to obtain a more precise estimate of the amount of learning, in order to establish an accurate baseline for comparison with full-current groups in tDCS Learning Experiments 2, 3 and 4. Additional testing was also performed using the same stimulation equipment in order to identify subject's baseline level of performance in this task before training (pretest), and to estimate the changes in performance immediately after training (immediate posttest) and again after a 1-hour delay (delayed posttest). Some subjects received additional training after this, to be described in subsequent manuscripts.

Experiment 3 examined the relationship between the amount of current administered using tDCS and the amount of learning. In Experiment 3, eight additional subjects were tested using the same methods employed in Experiment 2, but using an intermediate level of current, of 0.6 mA. For Experiment 4, the anode was placed over right parietal cortex in 12 additional subjects, centered at 10–20 electrode site P4, with current level set to 2.0 mA, and all other methods identical to Experiment 2.

Analysis of tDCS learning data

For Experiments 1–4, analysis of variance (ANOVA) was performed to test the effect of tDCS on the rate and amount of learning. For all experiments, the dependent variable was the percent of correct responses (either the correct detection of a concealed object or the correct response when no such object was present) during each of the four training blocks. For Experiments 2–4, dependent variables also included: (1) percent of correct responses in the pre-training test, (2)

percent of correct responses in the immediate post-training test, and (3) percent of correct responses in the immediate post-training test after a one-hour break period. Post-training test measures were baseline to the average percent of correct answers on the pre-training test. ANOVA was used to examine the effects of tDCS on the main effect of current strength (low- vs. full-current) and anodal electrode location (F10 vs. P4). A separate linear regression analysis was used to determine the relationship between the three levels of tDCS current (0.1 mA, 0.6 mA, and 2.0 mA) and changes in performance.

Results

Results of fMRI imaging study

Before training, increased blood oxygen level dependent (BOLD) responses to the perception of background scenes without concealed objects vs. inter-stimulus baseline (fixation cross) were highly significant across a wide range of brain areas (Fig. 2), including

much of bilateral occipital, temporal and parietal cortex, cerebellum, thalamus and lenticular nuclei (Table 1).

BOLD responses to scenes containing concealed objects were compared to those without, which revealed significant differences across a range of brain areas, including bilateral anterior caudate and putamen, occipital cortex, anterior and posterior insulae, parahippocampal gyri (BA 34), cingulate gyri (BA 31 and 32), superior temporal gyri, inferior and superior parietal lobules.

After training to the intermediate learning stage, a more restricted set of brain regions responded with significantly more positive BOLD response to scenes containing concealed objects vs. scenes without, located primarily in anterior brain areas. In addition, a set of posterior brain regions showed significantly more positive BOLD responses to scenes without concealed objects vs. those with, ranging in location from $x = +55$ to -33 , $y = -100$ to -67 and $z = -13$ to $+36$.

For the 7 subjects who were imaged after training to the expert learning stage, a more spatially restricted pattern of activity was found overall, with more positive BOLD response to scenes with concealed objects vs. scenes without extending from the left middle

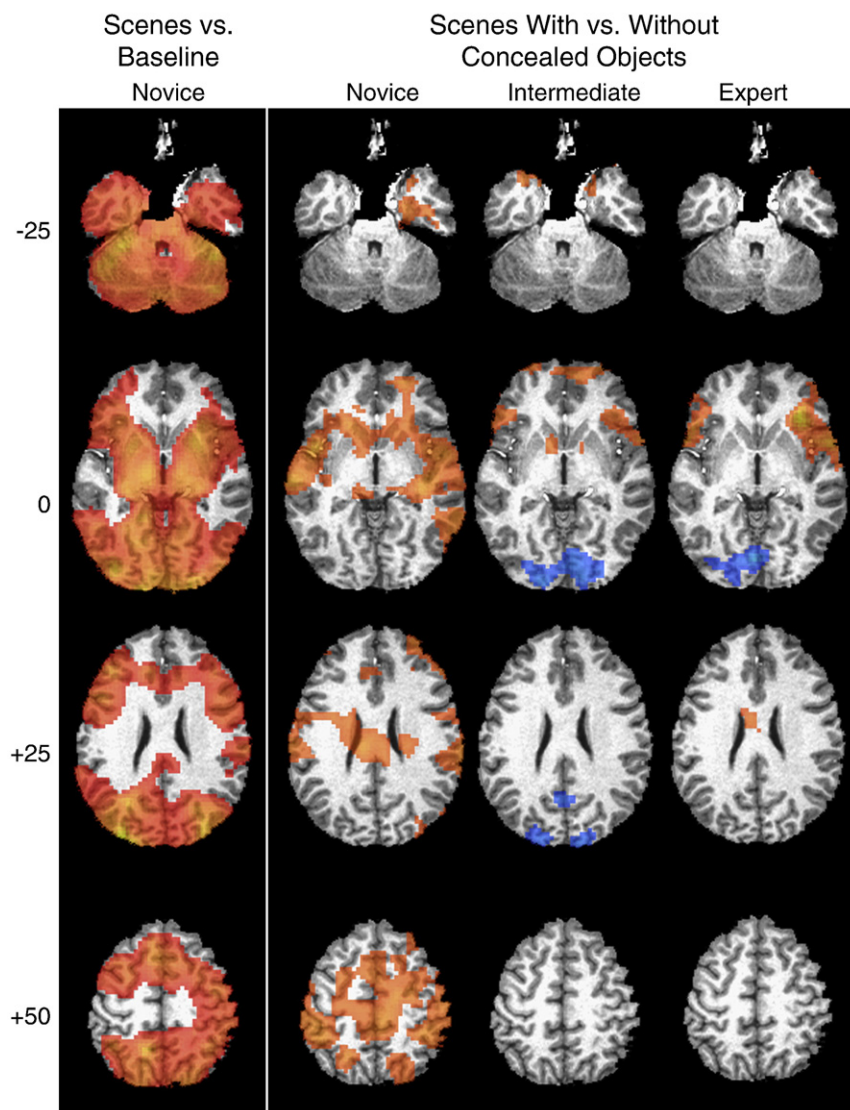


Fig. 2. BOLD fMRI responses to stimuli. The left hand column shows responses to scenes that do not contain concealed objects significantly greater than the inter-stimulus fixation crosshair for subjects at the novice learning stage, before training. The right three columns show activity for scenes containing concealed objects vs. stimuli that do not for subjects at the novice, intermediate and expert levels. Regions with more positive responses are shown in red to yellow, and regions with more negative responses are shown in blue to green. Locations of axial slices in Talairach coordinate system are shown. All images are thresholded with minimum voxel-wise $p < 0.05$, and the left of the subject is shown on the right of the image. Maximum threshold is $p = 1 \times 10^{-10}$ for the left hand column and $p = 1 \times 10^{-6}$ for the three right hand columns.

Table 1

Novice stage, background scenes without concealed objects vs. inter-stimulus baseline.						
Location	Max T value	P value	X	Y	Z	BA
Right thalamus	14.722	4.5×10^{-9}	+12	-12	0	
Left putamen	13.948	9.2×10^{-9}	-12	+3	0	
Left occipital	22.187	4.0×10^{-11}	-18	-93	-9	17, 18
Right occipital	19.458	2.0×10^{-10}	+18	-99	0	17, 18
Left middle occipital	23.743	2.0×10^{-11}	+33	-87	+9	18, 19
Right middle occipital	15.608	2.5×10^{-9}	-27	-96	+12	18, 19
Left fusiform	26.171	6.0×10^{-12}	-30	-54	-15	37
Right parahippocampal	21.515	6.0×10^{-11}	+24	-57	-6	19, 37
Novice stage, scenes with concealed objects > scenes without concealed objects						
Location	Max T value	P value	X	Y	Z	BA
Right superior temporal	5.557	1.2×10^{-4}	+63	-27	+9	22
Left middle temporal	4.982	3.2×10^{-4}	-48	+3	-15	21
Intermediate stage, scenes with concealed objects > scenes without concealed objects						
Location	Max T value	P value	X	Y	Z	BA
Right middle frontal	4.856	4.0×10^{-4}	+27	+66	+9	10
Right inferior frontal	4.816	4.2×10^{-4}	+27	+18	-18	47
Right inferior frontal	4.191	1.2×10^{-3}	+39	+27	-12	47
Left inferior frontal	4.591	6.2×10^{-4}	-30	+21	-18	47
Intermediate stage, scenes with concealed objects < scenes without concealed objects						
Location	Max T value	P value	X	Y	Z	BA
Left lingual	-4.658	5.5×10^{-4}	-9	-81	-9	18
Right middle occipital	-4.542	6.9×10^{-4}	+18	-90	+15	18
Expert stage, scenes with concealed objects > scenes without concealed objects						
Location	Max T value	P value	X	Y	Z	BA
Left inferior frontal	14.692	6.2×10^{-6}	-36	+33	+6	46
Right inferior frontal	6.848	4.7×10^{-4}	+45	+15	-9	47
Right cingulate	9.370	8.4×10^{-5}	+9	-12	+30	23
Right inferior parietal lobule	9.633	7.1×10^{-5}	+33	-33	+36	40
Expert stage, scenes with concealed objects < scenes without concealed objects						
Location	Max T value	P value	X	Y	Z	BA
Right lingual	-6.42	6.4×10^{-4}	+3	-78	-3	17, 18
Learning, novice to intermediate stages						
Location	Max $F_{(1,12)}$	P value	X	Y	Z	BA
Right middle frontal	79.06	1.3×10^{-6}	+48	+48	-9	47
Right medial frontal	26.84	2.3×10^{-4}	+3	+56	-10	10
Right parahippocampal	43.03	2.6×10^{-5}	+15	-12	-24	34
Right cingulate	34.56	7.5×10^{-5}	+9	-45	+30	31
Right middle temporal/right inferior parietal lobule	31.72	1.1×10^{-4}	+67	-40	-12	22, 39
Left superior temporal	21.45	5.8×10^{-4}	-48	-54	+12	39

Peak foci for contrasts are indicated. Locations are in Talairach coordinate system. BA indicates Brodmann's Area.

frontal gyrus to the superior temporal gyrus, and medially to the insula, along with other regions.

No significant BOLD response differences were found in the amygdala for scenes containing concealed objects that indicated possible threats vs. those without. At the expert learning stage, the difference between BOLD responses to stimuli with and without concealed objects in the right and left amygdala were $T=1.421$ and $T=1.122$, respectively. To examine the possibility that the amygdalae responded both to scenes with and without concealed objects, differences between scenes and inter-stimulus crosshair were examined. However, no significant differences were observed. Taken together, this suggests that the amygdalae are not sensitive to concealed objects that represent potential threats in this laboratory based study.

Effects of training

ANOVA was used to examine responses to concealed stimuli (concealed object present vs. absent) and training level (novice vs.

intermediate). The effects of training, in which responses to stimuli changed significantly with improved performance after training, were found primarily in the right hemisphere (Fig. 3), with the most significant focus located in right middle frontal gyrus.

Dynamic Bayesian network analysis

The DBN analysis was performed using fMRI data obtained at the novice and intermediate learning stages. DBN revealed some brain networks that were present both before and after training, and others that were only present after training. One network present before training included left supramarginal cortex and right caudate ($p=0.0014$) and another included right superior frontal and right ventral posterior cortex ($p=0.027$). Networks found after training but not before included a variety of brain regions. Three of these included right hippocampus, one combined with left middle frontal cortex ($p=0.027$), the second that included a combination of left fusiform and frontal middle orbital cortex ($p=0.036$), and the third

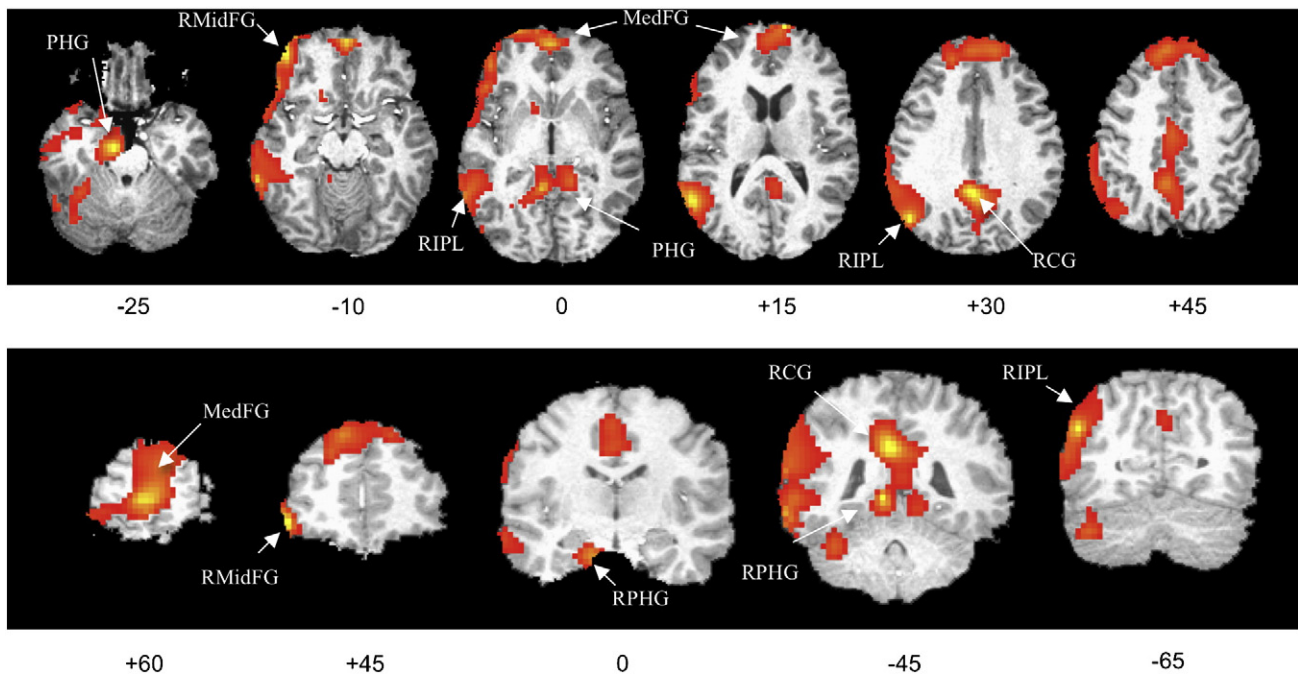


Fig. 3. Results of 2×2 ANOVA of training level (novice vs. intermediate) and stimulus type (camouflaged cue present vs. absent). Significant F values for training level effect are shown. Arrows indicate significant foci in parahippocampal gyri (PHG), right middle frontal gyrus (RMidFG), right inferior parietal lobule (RIPL), medial frontal gyrus (MedFG) and right cingulate gyrus (RCG). Axial images shown in top row, coronal images shown in bottom row. Locations of axial slices in Talairach coordinate system are shown. All images are thresholded with minimum voxel-wise $p < 0.05$, with maximum threshold of $p = 1 \times 10^{-4}$.

with left middle temporal cortex ($p = 0.041$). Another network included right fusiform and right inferior parietal cortex ($p = 0.029$).

This imaging study was followed by a series of behavioral learning studies using tDCS. Based on the published literature of object perception and selective attention, and the results of our fMRI studies of concealed object detection described earlier, we chose the right inferior frontal (found to be most significant using GLM-based methods) and right parietal brain areas (found using DBN) as the most accessible targets for brain stimulation with the highest likelihood of accelerating the learning process.

Results of tDCS learning studies

A total of 83 healthy participants (mean age 24.1 years, range 18 to 38 years, 53 male, 30 female) performed the same learning task with different groups of participants receiving varying levels of tDCS current over different scalp locations. For all tDCS learning studies, a series of four, 12-minute long training blocks were presented during the one-hour learning phase (see Fig. 1), with tDCS applied during the first two training blocks. For tDCS Learning Experiments 1 and 2, anodal current was applied over the right inferior frontal scalp, located nearby electrode site F10 over the right sphenoid bone, or right temple, with the cathode on the contralateral arm. For 26 subjects in the “full-current” tDCS group, 2.0 mA of current was used. In 37 subjects in the “low-current” tDCS group, 0.1 mA current was used.

Fig. 4 shows the change in accuracy obtained across the four, 15-minute training blocks in Experiment 1 and replication of this in a separate group of subjects in Experiment 2. For both Experiments 1 and 2, subjects receiving full-current reached 77% mean accuracy by the 4th training block. The 13 subjects receiving low-current in Experiment 1 reached 69.4% accuracy (SE 3.3%), and the 23 subjects receiving low-current in Experiment 2 reached 67.5% accuracy (SE 3.4%), which was not significantly different between experiments ($F_{(1,35)} = 1.01$, N.S.). Subsequently, data were pooled across both experiments for analysis. During training, accuracy changed

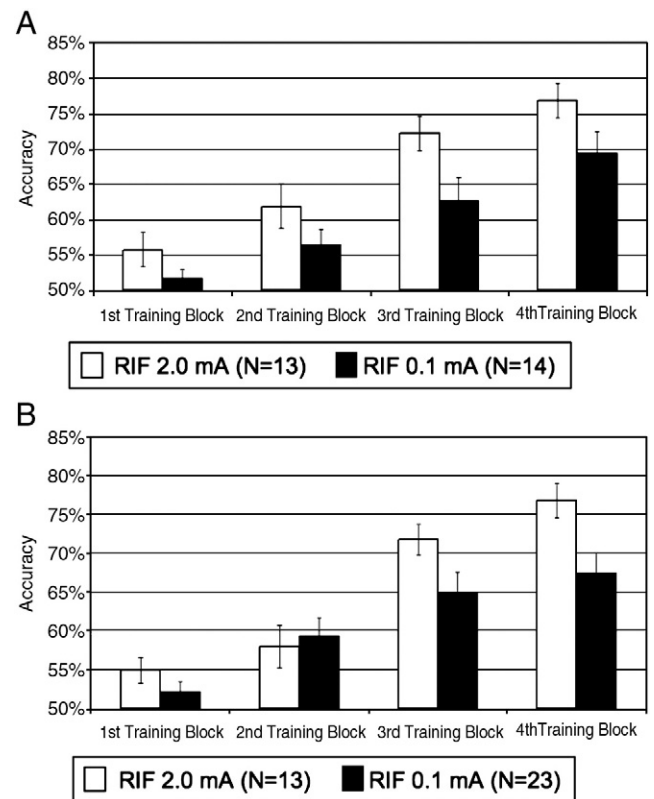


Fig. 4. Shows change in accuracy with training across the four tDCS training blocks for tDCS Learning Experiments 1 and 2. Mean accuracy within each training block is indicated for subjects receiving full-current (2.0 mA) tDCS over right inferior frontal cortex (white columns) and for subjects receiving low-current (0.1 mA) tDCS (black columns). Standard errors are shown. A. Shows results for tDCS Learning Experiment 1. B. Shows results for tDCS Learning Experiment 2, which used the same current strength and electrode placement as in tDCS Experiment 1, in a different group of subjects. The effect of tDCS current was not significantly different across the two groups of subjects.

significantly across the four training blocks in both the full- and low-current tDCS groups of Experiments 1 and 2 ($F_{(3,183)} = 89.86$, $p = 8.78 \times 10^{-36}$). The 26 subjects receiving full-current tDCS learned significantly more over the 1 h of training, compared with the 36 subjects receiving low-current tDCS, as shown by the difference in accuracy between groups during the final training block ($F_{(1,61)} = 13.16$, $p = 5.86 \times 10^{-4}$).

For the 36 subjects in Experiment 2 (23 of these subjects receiving low-current tDCS and 13 receiving full-current tDCS), detection accuracy was tested immediately before training, immediately after training, and then again after a one-hour rest period. Pre-training test data were obtained in order to ascertain baseline levels of accuracy resulting from prior experience before training, and to verify that these stimuli were impossible to discriminate without training. Before training, accuracy was close to chance (50.75% mean accuracy, SE 0.64%), confirming that scenes containing concealed objects were initially indistinguishable from scenes without concealed objects, and that training was required to perform this task.

Subjects receiving low-current tDCS improved their accuracy by 14.2% (SE 2.84%) between the pre-training and immediate post-training test blocks, as shown in Fig. 5. Accuracy decreased to 10.5% (SE 2.66%) between the pre-training and delayed post-training test blocks, after a one-hour rest period. When full-current tDCS was applied during training, this resulted in a 26.6% (SE 2.51%) increase in accuracy immediately after training relative to before training. This was an 87% greater increase in performance accuracy with training relative to that found for the low-current tDCS group ($F_{(1,35)} = 12.23$, $p = 0.001$). After the one-hour delay, mean accuracy for the full-current tDCS group was 21.3% (SE 1.87%). There were no significant differences between the full-current and low-current groups in the amount of forgetting over the one hour delay, as determined by the reduction in accuracy over the 1-hour interval between the immediate and 1 hour delay post-tests ($F_{(1,35)} = 0.199$, N.S.). This

suggests that the greater increase in performance obtained with training in the full-current tDCS group did not degrade more quickly than the low-current tDCS group after training was ended. The greater amount of learning during training for the full-current group, combined with a similar amount of forgetting between groups after this, resulted in an overall increase in between-group learning differences by the end of the 1 hour rest period, or 104% greater change in performance accuracy ($F_{(1,35)} = 11.09$, $p = 0.002$).

TDCS Learning Experiment 3 tested the hypothesis that the amount of learning would scale with tDCS current strength. All subjects from Experiments 2 and 3 were entered into a regression analysis using current as an independent variable. Performance accuracy of the 8 subjects that received intermediate-current (0.6 mA) over right inferior frontal cortex (16.8%, SEM 3.0%) fell between the low- and full-current groups. This relationship between current strength and learning as measured by change in performance with training was well predicted by a linear model of current strength ($r = 0.437$, $p = 0.0015$). This suggests that there was a strong relationship between the amount of current administered during training and the amount of learning, within the range of current strengths tested here.

In tDCS Learning Experiment 4, we examined the effect of full-current anodal tDCS over right parietal cortex (over electrode site P4) in 12 additional subjects, and compared this to full-current and low-current anodal tDCS over right inferior frontal cortex from Experiment 2. There was a significant effect of tDCS over electrode site P4 on learning, improving accuracy by 22.5% (SEM 2.6%; $F_{(1,34)} = 4.40$, $p = 0.035$) relative to low-current stimulation over F10. This magnitude of learning acceleration was somewhat smaller for P4 relative to full-current F10 stimulation immediately after training ($F_{(1,25)} = 3.46$, $p = 0.075$). No significant difference between P4 and F10 full-current tDCS was present by the 1-hour delayed posttest.

Relationship between skin sensation and learning

Although subjects were blind to the presence of a manipulation of current intensity, and were naïve to tDCS upon entering the study, differences in skin sensation between groups may have influenced results, through differences in level of distraction or arousal, or some other indirect mechanism. To examine the relationship between self-reported skin sensation and learning, we collected skin sensation data from 73 subjects. While there were significant differences in self-reported skin sensation between the full-current and low-current groups ($F_{(4,68)} = 6.30$, $p = 0.003$), learning rate was not associated with sensation ($F_{(3,195)} = 0.541$, N.S.). Taken together, this suggests that while skin sensation did vary with current amplitude, individual differences in reported skin sensation had no relationship with learning rate. This suggests that tDCS may have an effect on behavior through a direct effect on neural activity, rather than indirectly through stimulation of the skin.

Discussion

Functional MRI and tDCS were combined to elucidate brain mechanisms underlying the process of learning to recognize disguised and concealed objects placed in simulated naturalistic settings. We present the main findings of these studies: (1) Subjects performed near chance before training, and learning was required to perform this task. (2) Before training, a large number of brain regions were found that responded more to correctly identified scenes with concealed objects than to scenes without. (3) After training, a smaller but more significant pattern of activity was found primarily in anterior brain areas, while posterior occipito-temporal regions responded more to scenes without concealed objects. (4) Training to intermediate performance was correlated with significant changes in activity of right middle and inferior frontal gyri, along with medial and superior temporal, cingulate and parietal regions located primarily within

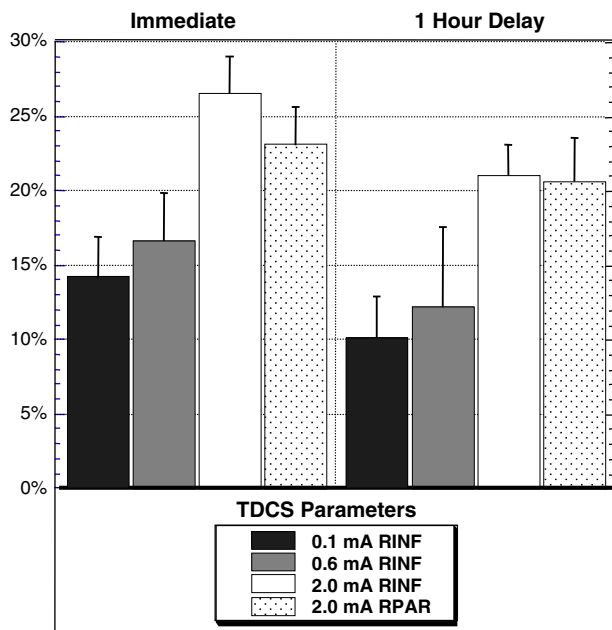


Fig. 5. Shows difference in accuracy obtained with training across the four tDCS conditions for tDCS Learning Experiments 2–4. Columns shown on the left side of the figure show changes in accuracy immediately after training, columns on the right side of the figure show changes in accuracy 1 h after training, both compared to the level of accuracy found immediately before training. Current strength (0.1 mA, 0.6 mA and 2.0 mA) and electrode location indicated: right inferior frontal (RINF) and right parietal (RPAR). The amount of learning during training was sensitive to current strength and to electrode location. No effects of tDCS current or electrode location were found on the rate of forgetting between tests collected immediately after training and after a 1 hour delay.

the right hemisphere. (5) DBN analysis revealed a number of brain networks including medial temporal, frontal and parietal regions that were present after training but were not observed before. (6) tDCS over right inferior frontal cortex increased performance during and immediately after training relative to a low-current control condition. (7) This difference grew to a factor of two after a one-hour delay, 90 min after tDCS was ended, suggesting that improved performance was not a transient effect of tDCS. (8) Improvement in accuracy was proportional to the level of tDCS current administered during training. (9) tDCS over right parietal cortex also resulted in improved accuracy, with nearly identical magnitude of effects found after a one hour delay.

The strong positive relationship between the level of activity in right inferior frontal cortex and improved behavior, found both through a correlation with imaging data across stages of learning and through the effects of anodal stimulation over this region using tDCS, supports our hypothesis that this region is involved in performance of this task. The validity of these tDCS results is supported both by replication in separate samples of subjects, and by the finding of a dose–response effect of tDCS current strength on performance after training. Also, the finding that anodal stimulation over right parietal cortex increases learning supports the results of our DBN analysis.

Neural and cognitive mechanisms of tDCS effects on learning

TDCS over right inferior frontal and right parietal cortex led to a large increase in learning. One hypothesis to explain these results is that the greater perceptual load required to correctly identify scenes containing concealed objects results in additional demands on cognitive processes supported by these brain regions. One candidate cognitive process that involves the set of regions found here, and is likely to be involved in identifying concealed objects, is attention. Attentional processes could assist in the identification of concealed objects by applying information gained in previous learning trials and by reducing the influence of distracter objects and features on perception, in order to guide the selection of features and objects required for identification. Attention involves both bottom-up or exogenous processes that are driven by stimulus characteristics, and top-down or endogenous processes where features and objects are selected in part based on the prior experiences and current goals of the observer (Hillyard et al., 1973; Parasuraman, 1998; Posner, 1980). It follows that exogenous attentional systems may be more susceptible to the confusion generated by obscured and concealed objects in complex visual environments, whereas endogenous attentional systems may facilitate their perception. One prediction of this model is that improved performance would be associated with increased BOLD activity in regions mediating endogenous attention, as described earlier, and also reduced BOLD activity in regions mediating exogenous attention, which is supported by our finding of relatively reduced responses in occipito-temporal cortex evoked by scenes with concealed objects vs. scenes without, in opposite direction to the change with learning found in frontal cortex.

Another hypothesis that may explain the present results is a direct effect of tDCS on neural plasticity. Using dextromethorphan, an NMDA receptor-blocker, Liebetanz et al. (2002) found a reduction in tDCS effects, which suggests that tDCS may interact with glutamatergic systems to produce behavioral change. Glutamatergic systems have been found to be important for learning (Bliss and Collingridge, 1993). Therefore, tDCS may enhance learning by alteration of glutamatergic-associated neural plasticity, or some other affect on neurochemistry. Separate studies in our laboratory to examine these cognitive and neurochemical hypotheses are ongoing (Clark et al., 2010).

Comparisons among methods to improve skill learning and expertise

TDCS and TMS have been found affect other types of learning, including motor (Antal et al., 2004; Flöel et al., 2008; Galea and Celnik,

2009; Nitsche et al., 2003; Reis et al., 2009a,b), somatosensory and visual motion perception (Ragert et al., 2008; Stewart et al., 1999; Tegenthoff et al., 2005) and words (Boggio et al., 2009; Gallate et al., 2009; Marshall et al., 2004). While important, these findings are of limited generalizability to objects and scenes that we typically encounter in everyday life. To our knowledge, no prior studies have attempted to use brain stimulation in order to accelerate learning of complex visual stimuli of the type found in natural scenes as we have done here.

The present results suggest that tDCS guided using neuroimaging may have a large impact on the rate of learning relative to other methods. For instance, meta-analyses of the last two decades of published experiments on adult cognitive training methods yield a sample weighted mean Cohen's *d* for learning of 0.63 with an average increase in learning of about 20% (Arthur et al., 2003). Cohen's *d* in the present brain stimulation study was found to be 1.2, with a doubling of learning, which is much higher than found for most purely cognitive training methods. Other neuroscience-based manipulations found to increase learning include manipulating blood levels of estrogen (Korol and Kolo, 2002) and glucose (Manning et al., 1998) and manipulations that alter cholinergic (Levin, 1992), gabaergic (Collinson et al., 2002) and noradrenergic function (Breitenstein et al., 2004; Feeney and Westerberg, 1990), as well as caffeine (Smith, 2002), and curcumin (Frautschy et al., 2001) among a variety of others. As with cognitive training methods, tDCS as employed here may provide a larger benefit to learning compared with these other methods, although differences in the type of learning performed in each study may confound direct comparison. Compared with pharmacological treatments, tDCS has the advantage of potentially superior safety though its more precise anatomical specificity, and the capability of ending treatment quickly if required.

Applications of tDCS for improved learning

Learning to interpret perceptual information quickly and accurately in a complex natural environment is essential for acquiring many forms of expertise. This includes common activities such as driving, and specialized types of expertise such as interpreting radiological imaging data, identifying objects in photos and surveillance images, piloting aircraft and operating other complex machinery, and identifying threats such as snipers and bombs in a wartime environment, among a wide variety of other everyday and work-related skills. Researchers in human factors, education, and related fields such as instructional technology design have examined the efficacy of a number of different training techniques for enhancing learning in such domains. However, such efforts have often not been informed by knowledge on brain mechanisms of learning. The results of the present studies provide critical new information on the brain networks involved in learning to identify concealed objects. These tDCS results point to the potential for the development of an effective new training technology for work-related training. With some modifications, the tDCS methods developed here might lead to improved methods of training for many real-world skills.

Neural and cognitive mechanisms of concealed object detection

In evolutionary terms, an important goal of object perception is the rapid and accurate response to cues present in the environment that indicate possible sources of danger, food or other circumstances, and avoiding perceptual errors with potentially serious consequences. Naturalistic surroundings typically contain more information or clutter than perceptual systems can identify at one time (Broadbent, 1958; Neisser, 1967; Schneider and Shiffrin, 1977; Tsotsos, 1990; although see also Peelen et al., 2009). This limitation requires that perceptual resources be directed towards more salient features and away from less important information in a process mediated by

attention. This suggests that brain regions mediating endogenous attention, including frontal, parietal and temporal regions, may provide resistance to this perceptual confusion and facilitate the perception of concealed objects.

This relationship between activity in areas mediating endogenous attention and performance in tasks involving object detection is supported by a number of prior studies that suggest an important role for frontal, parietal, middle and superior temporal areas in object categorization and visual search tasks (Beauchamp et al., 2004; Clark et al., 1996; Coull et al., 1996; Maguire et al., 2001; Fan et al., 2005; Buschman and Miller, 2007; Cabeza et al., 2008) and in attentional networks that facilitate the classification of objects (Clark and Hillyard, 1996; Posner and Peterson, 1990), extraction of categorical information from objects (Freedman et al., 2001; Nieder et al., 2002), and other relevant cognitive processes (Ericsson and Staszewski, 1989; Miller et al., 1996; Rao et al., 1997). It follows that these brain networks may contribute to the recognition of hidden and concealed objects, in part by supporting endogenous attentional processes required to perform these tasks.

The concealed objects indicated potential threats in this virtual environment. Prior studies have found that anticipation and avoidance of overt threats involves brain networks overlapping or nearby those found in the present study, primarily including the amygdala, along with insula, cingulate, parietal, hippocampal and frontal regions (Benuzzi et al., 2008; Delgado et al., 2009; Kim et al., 2006; Nitschke et al., 2006; Simmons et al., 2004; Straube et al., 2007). However, no amygdala response was found in the present study, suggesting that the threat-relatedness of the concealed threat-related objects used here did not illicit an overt “fear” response. However, the concordance of the other brain regions between the present and previous studies suggests that overt threat-related stimuli might have increased activity in these other brain regions in part due to their greater salience, leading to increased attention (Mesulam, 1999). If true, this effect on attention could explain the similarity of results between overt threats examined in prior studies and concealed threat-related objects examined here.

The finding of greater right inferior frontal response at the intermediate learning stage moving to left inferior frontal response at the expert learning stage is also interesting in a number of respects. This may result from right hemisphere dominance for processing of stimulus novelty and attentional processing at early stages of learning (Heilman and Van Den Abell, 1980). This also suggests that once an expert performance stage is reached, subjects may employ a verbal strategy to mediate performance of this task. This possibility is supported by a number of prior studies that have examined indirect social and cognitive mechanisms for learning to recognize and respond to threats based on verbal and social information (Askev and Field, 2008; Dymond and Roche, 2009; Olsson and Phelps, 2007). This also suggests that application of tDCS to left frontal regions, rather than right, may facilitate later stages of learning in the concealed object-learning task used here.

Evolutionary history of concealed object detection

Cryptic shape, coloration and patterns of movement decrease the risk of detection for all types of animals (Cott, 1940; Edmunds, 1974). The better an animal matches its surroundings, or disguises itself as another type of object, the less likely it is to be accurately identified by an observer (Cott, 1940; Edmunds, 1974; Edmunds, 1990; Endler, 1992; Guilford, 1992; Merilaita, 2003; Norris and Lowe, 1964) which increases its chances for survival. It follows that the prey or predators of an animal using crypsis would need to improve their ability to accurately perceive concealed animals in order to increase their own chances of survival. While generally understood, details of how such methods of concealment interact with brain systems mediating perception, attention and memory have not been well studied.

Given the possibly strong influence of crypsis on the evolutionary development of our cognitive and perceptual systems, further study may be warranted.

Previous studies have examined neural aspects of perceptual processing associated with concealment, such as partial occlusion, illusory contour and stimulus fragmentation (Ffytche and Zeki, 1996; Hirsch et al., 1995; Kourtzi et al., 2005; Larsson et al., 1999; Murray et al., 2002; Seghier et al., 2000) and object perception in the presence of noise (Dolan et al., 1997). These studies have found responses mostly in posterior cortical regions specialized for feature processing, which contrasts with our results. In one previous study, Sehatpour et al. (2008) identified lateral frontal areas responding to whole vs. scrambled images. They hypothesized a convergent model for closure processing whereby feed-forward processes conveying perceptual information from posterior sensory areas converged with feedback projections from frontal areas, limiting the number of possible matches with a set of stored representations, in a process mediated by endogenous attention, which is in agreement with our data.

Conclusions

The ability to detect concealed objects in complex, naturalistic surroundings is critical for the effective performance of many skills required for everyday and specialized work tasks. Using a variety of novel methods, we were able to apply tDCS to reduce the time required to learn this skill. These methods included using naturalistic stimuli from a virtual reality environment that is currently in use for training, and employing an unassisted discovery-learning paradigm, which helped to capture the complexity and dynamics of behavior as it occurs naturally. Another critical feature of our methodology was the combined use of neuroimaging and brain stimulation. Neuroimaging was used to identify placement of tDCS electrodes, and tDCS was then used to verify the contribution of these brain regions to this task through increased performance and rate of learning.

While the development of our ability to detect animals using crypsis probably had a strong influence on the development of the perceptual and attentional systems we have today, few previous neuroimaging studies have examined this capability. Our fMRI studies suggest that right inferior frontal and parietal cortex, along with temporal, cingulate and other brain regions, are involved in learning to perceive concealed threat-related objects in naturalistic environments. TDCS over right inferior frontal and right parietal cortex greatly improved learning and performance, further supporting these findings. Through this combined brain imaging and stimulation methodology, a large increase in learning was found, as revealed through increased performance after a set period of training. Considering its safety, low cost, and simplicity, along with its apparent effectiveness for increased learning, tDCS guided with neuroimaging may offer the potential to benefit training for real-world expertise.

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