Effects of non-invasive brain stimulation on associative memory

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Abstract

Associative memory refers to remembering the association between two items, such as a face and a name. It is a crucial part of daily life, but it is also one of the first aspects of memory performance that is impacted by aging and by Alzheimer's disease. Evidence suggests that transcranial direct current stimulation (tDCS) can improve memory performance, but few tDCS studies have investigated its impact on associative memory. In addition, no prior study of the effects of tDCS on memory performance has systematically evaluated the impact of tDCS on different types of memory assessments, such as recognition and recall tests. In this study, we measured the effects of tDCS on associative memory performance in healthy adults, using both recognition and recall tests. Participants studied face-name pairs while receiving either active (30 minutes, 2 mA) or sham (30 minutes, 0.1 mA) stimulation with the anode placed at F9 and the cathode placed on the contralateral upper arm. Participants in the active stimulation group performed significantly better on the recall test than participants in the sham group, recalling 50% more names, on average, and making fewer recall errors. However, the two groups did not differ significantly in terms of their performance on the recognition memory test. This investigation provides evidence that stimulation at the time of study improves associative memory encoding, but that this memory benefit is evident only under certain retrieval conditions.

Keywords: tDCS, Associative Memory, Recall, Recognition

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1. Introduction

Associative memory refers to memory for the association or relationship between two items. Everyday examples include remembering a person's name or remembering where you left your car keys. In a typical associative memory experiment, participants study pairs of items, such as face–name pairs, and are tested on their memory for the pairings via recognition or recall tests. In recognition tests, the participants are shown studied pairs as well as lures in which studied pairs are recombined to form novel pairings. Accurate performance requires that participants successfully identify studied pairs while rejecting the novel pairs. In recall tests, participants are shown a cue (e.g., a face) and are asked to generate the other member of the pair (e.g., the name). In both the recognition and recall tasks, successful performance requires the participant to accurately recollect the association between the members of the studied pairs; that is, participants must remember that *this* face was paired with *that* name. In this investigation, we seek to improve this type of memory using a noninvasive brain stimulation technique.

Transcranial direct current stimulation (tDCS) is a brain stimulation technique that can modulate neuronal activity at the site of stimulation (Nitsche & Paulus, 2000). Stimulation is thought to produce a two-fold effect – an acute modulation of cortical excitability (Nitsche & Paulus, 2000) followed by lasting effects that are NMDA-receptor dependent (Liebetanz, Nitsche, Tergau, & Paulus, 2002) and therefore similar to long-term potentiation (LTP) and long-term depression (LTD) processes posited to underlie learning and memory (Rioullet-Pedotti, Friedman, Hess, & Donoghue, 1998). Recent studies have shown that tDCS can improve cognitive performance in both clinical populations and healthy adults on tasks ranging from

motor learning to decision making (Coffman, Clark, & Parasuraman, 2014; Dayan et al., 2013; Manenti, Cotelli, Robertson, & Miniussi, 2012). Many of these studies have focused on working memory (Fregni et al., 2005; Ohn, et al., 2008) or episodic memory (e.g., Chi et al., 2010; Javadi & Walsh, 2012), and the majority of this work suggests that tDCS can improve performance. However, other studies find little or no benefit from tDCS (e.g., Elmer, Burkard, Renz, Meyer, & Jancke, 2009), suggesting that conditions under which memory might improve are not yet fully understood.

Although associative memory is critically important for learning and for navigating everyday life, few studies have explored whether or not tDCS can enhance associative memory performance. Some prior studies have incorporated associative learning paradigms into investigations of the effects of tDCS effects on language learning (Fiori et al., 2011; Flöel, Rosser, Michka, Knecht & Breitenstein, 2008). In those paradigms, participants were asked to learn novel, nonword names for common objects. These studies have shown that tDCS with the anode placed on the scalp over left Wernicke's area improved reaction times in a recall task (Fiori et al., 2011) and performance on an incidental language learning task (Flöel et al., 2008). However, stimulation applied to the same location has been shown to improve reaction times in a picture naming task (Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008), making it unclear whether the improved performance seen in these studies was due to enhancement of associative memory or to facilitation of lexical access.

There is one study that suggests that tDCS may improve associative memory as measured by recall, but not recognition (Flöel et al., 2012). In this study, older adults learned object-location associations in an incidental learning paradigm while active or sham tDCS was applied with the anode positioned over the right temporoparietal cortex. Participants performed better on

a delayed recall test (one week after learning) following active stimulation. Interestingly, although tDCS improved recall performance, it had no effect on learning rates at the time of study. The incidental learning task, in which participants were presented with correct pairs (frequently) and incorrect pairs (infrequently), was functionally similar to a recognition memory task, particularly in the later blocks of the task when the participants had become familiar with the correct object-location pairings. Since active tDCS enhanced the encoding of the associations as measured by delayed recall, we might also expect it to enhance recognition performance during the learning task. The fact that it did not hints at the possibility that tDCS has differential effects on recognition and recall tests of associative memory. However, this prior research was not explicitly designed to test recognition memory performance, so the reasons for this difference are unclear.

Studies of other types of memory (i.e. item memory) have found tDCS-induced improvements as measured by both recognition and recall tests. Studies of recognition memory have found that tDCS with the anode positioned over the left superior parietal cortex improved recognition memory for studied words (Jacobson, Goren, Lavidor, & Levy, 2012), while tDCS with the anode located above the right anterior temporal lobe (ATL) reduced false alarms in a shape recognition task (Chi, Fregni, & Snyder, 2010). Studies investigating the timing of stimulation with respect to encoding and retrieval suggest that tDCS has a bigger impact on memory if it is applied at the time of study. For instance, Javadi and Walsh (2012) showed that recognition memory improved when tDCS was applied during encoding, but that memory improvements were only marginal when tDCS was applied during retrieval. Similarly, Javadi, Cheng, & Walsh (2012) applied stimulation with the anode above the left dorsolateral prefrontal cortex (dlPFC) either during stimulus presentation or immediately after. Results showed that

both recognition performance and reaction times were improved when stimulation was applied in a short burst at the beginning, but not at the end, of study trials. Overall, these findings show that tDCS applied during study improves recognition memory performance in healthy adults.

Only a few studies have investigated the effects of tDCS on recall, but these studies have also found improvements in memory performance. In one experiment (Penolazzi et al., 2010), participants studied positively and negatively valenced images while receiving stimulation with the anode placed over the right or left frontotemporal cortex. Right hemisphere stimulation improved participants' recall for the positive images while left hemisphere stimulation improved recall for the negative images. Another study found that recall of category exemplars was improved when stimulation was applied to both the left and right dlPFC during a consolidation interval (while the participant slept; Marshall, Mölle, Hallschmid, & Born, 2004). TDCS has also been shown to reduce rates of false recall (i.e., producing an item not previously studied; Boggio et al., 2009). As was the case with recognition, these results suggest that stimulation improves recall both by increasing the number of items a participant can recall and by reducing the number of memory errors.

In summary, studies investigating memory indicate that tDCS can improve performance as measured by both recognition and recall tasks. However, few studies have tested the effects of tDCS on associative memory performance, and no studies to date have systematically examined the effects of tDCS on both recognition and recall performance in a single experiment. It is not currently known whether tDCS has different effects on these two common measures of memory performance.

In this experiment, we assessed the effects of tDCS on associative memory, as measured by both recognition and recall tests. To test the effects of tDCS on associative memory, we chose

to position the anode above the left inferior frontal gyrus (LIFG). Past functional magnetic resonance imaging (fMRI) experiments on face-name associative memory have found that activity in the LIFG at the time of study is associated with successful memory (Sperling et al. 2003b) and fMRI guidance has been used effectively in prior tDCS accelerated-learning paradigms (e.g., Clark et al., 2012). Participants in this experiment received either active or sham tDCS while studying face-name pairs and then completed both recognition and cued recall tests (**Figure 1**). We predicted that stimulation would lead to improved memory performance relative to sham stimulation on both recognition and recall tests, consistent with prior reports (e.g., Chi, Fregni, & Snyder, 2010; Jacobson et al., 2012; Marshall et al., 2004; Penolazzi et al., 2010). Finding that tDCS improves associative memory performance on both measures would suggest that stimulation effects are robust, and affect memory regardless of how one attempts to retrieve the stored information.

We also considered the possibility that tDCS would improve associative memory performance as measured by recall tests, but not recognition tests. The prior work using associative learning paradigms have found mixed results in which tDCS improved recall performance, but not performance on the recognition-based learning task (Flöel et al., 2012). In addition, prior work that has examined interventions to improve memory has found memory improvements when performance is measured by recall but not when measured by recognition (Payne & Roedigger, 1987), suggesting that the nature of the memory test one employs may affect the ability to detect memory improvements.

Finally, because we used face-name pairs as to-be-encoded stimuli in this investigation, we examined differences in associative memory performance that were related to characteristics of the faces. Prior research suggests that memory is superior for faces of one's own age group

(own-age bias; Rhodes & Anastasi, 2012), gender (own-gender bias; Wright & Sladden, 2003), and ethnicity (own-ethnicity bias; Gross, 2009). While all of the face stimuli used in the current study were of the same ethnicity, the age and gender of the faces varied. Each participant viewed equal numbers of faces from each age group (young, middle aged and elderly) and each gender, allowing us to test the effects of stimulation on own-age and own-gender bias.

2. Results

2.1 Memory performance on the baseline test

On the baseline memory test, there were no significant differences in performance between the active and sham groups. On average, the participants in the active stimulation group had an 84.7% hit rate (a response of “1” or “2”; $SD = 21.6\%$) for the old face-name pairs and a 15.3% rate of misses (a response of “3” or “4”). They correctly rejected 74.3% ($SD = 16.1\%$) of the lures, and falsely identified 25.7% of the pairs as old. The participants in the sham group had an 88.9% hit rate ($SD = 10.8\%$) for the old items and a false alarm rate of 38.2% ($SD = 16.5\%$). The accuracy of the two groups was not significantly different for either the old items ($t(22) = 0.60$, Cohen’s $d_s = 0.24^1$) or for the lures ($t(22) = 1.88$, $p = 0.07$, $d_s = 0.75$). On the recall test, the participants in the active group correctly recalled 42.4% ($SD = 21.9\%$) of the names, on average, while the sham group correctly recalled 36.3% ($SD = 13.3\%$; $t(22) = 0.35$). The performance of the two groups was not significantly different ($t(22) = 0.81$, $p = 0.21$, $d_s = 0.33$).

2.2 Study Phase

Participants in the active stimulation group were slightly more likely to say that the names fit the faces (73.7%, $SD = 14.8\%$) than the participants in the sham stimulation group (69.4%, $SD = 23.1\%$), but this difference was not significant ($t(22) = 0.53$, $d_s = 0.22$). The

¹ All effect sizes were calculated using the tool developed by Lakens (2013).

average task response times were 0.83 seconds for the active group and 0.89 seconds for the sham group. This difference was not significant ($t(22) = 0.74$, $d_s = 0.30$).

2.3 Recognition Test

The recognition performance of the two groups was quite similar. The proportions of each response type for each condition are shown in **Figure 2**. On average, the participants in the active stimulation group had a 76.9% hit rate (SD = 14.4%) for the old face-name pairs and correctly rejected 70.0% (SD = 17.5%) of the recombined pairs. Participants in the sham group had a 75.7% hit rate (SD = 13.1%) and correctly rejected 67.1% of the lures (SD = 16.3%). None of these between-group differences reached significance (all t s < 0.40). We also examined the recognition memory responses based on the participants' ratings of the fit between the face and the name at study. There were no significant differences in memory performance between the good fit (i.e., where the name "fit the face") and the poor fit trial types for either the active or sham stimulation groups (all t s < 0.66, all p s > 0.26).

To determine whether or not the two groups differed in their ability to discriminate between old pairs and recombined pairs, the participants' responses were used to calculate d_a scores. These scores provide a measure of discrimination between old and new items that is similar to d' , but that takes the participants' full response scale (1-4, reflecting yes/no as well as sure/unsure responses) into account, making it a more appropriate measure of discrimination for this task (see Matzen & Benjamin, 2009). Participants' ratings of the old and recombined pairs were used to generate receiver operating characteristic curves (ROC curves) and the d_a score represents the shortest distance from the origin of a two-dimensional space to the ROC curve when plotted in normal-deviate coordinates, scaled by a constant (see also Banks, 2000; Benjamin, Diaz & Wee, 2009). A higher d_a score indicates that a participant was better able to

discriminate between old and new pairings. The d_a scores were calculated using RscorePlus (Harvey, 2010). Participants in the active stimulation group had an average d_a score of 1.42 while the participants in the sham group had an average d_a score of 1.28. Discrimination performance did not differ significantly between the two groups ($t(22) = 0.58$, $d_s = 0.24$).

The participants in the active stimulation group had slightly faster average reaction times than the participants in the sham group (3.2 seconds versus 3.7 seconds). However, this difference was not significant ($t(22) = 1.07$, $p = 0.15$, $d_s = 0.44$).

2.4 Recall Test

The participants' average performance on the recall test is shown in **Figure 3**. There was a broad range of performance on the recall test, with recall rates for participants in the active group ranging from 10 to 41 correct recollections and performance for participants in the sham group ranging from 5 to 34 correct recollections. Participants in the active group recalled an average of 26.3% (SD = 12.1%) of the studied names, while the participants in the sham group recalled an average of 17.1% (SD = 11.1%). The items on the recall test were divided into three groups based on the conditions in which the pictures appeared on the recognition test. Twenty-four of the faces had been tested as part of old pairs in the recognition memory test, 24 had been tested as part of recombined pairs in the recognition test, and 24 had not appeared in the recognition memory test. The participants in the active group correctly recalled the names for an average of 42.2% (SD = 20.3%) of the faces that had been tested in old pairs on the recognition test while the participants in the sham group correctly recalled an average of 28.6% of those names (SD = 17.1%). For the faces that had been presented as lures on the recognition test, the participants in the active group successfully recalled 14.3% (SD = 8.3%) of the originally studied names while participants in the sham group recalled 12.2% (SD = 9.2%). For the faces that did

not appear on the recognition test, participants in the active group recalled 22.6% of the studied names ($SD = 13.7\%$) and the participants in the sham group recalled 11.3% ($SD = 10.0\%$).

A 2x3 ANOVA (stimulation condition x recognition test presentation condition) on recall rates showed that there was a significant main effect of stimulation condition ($F(1,66) = 7.64, p < 0.01, \eta^2 = 0.18$) and a main effect of recognition test condition ($F(2,66) = 17.70, p < 0.01, \eta^2 = 0.82$). There was not a significant interaction between the two ($F(2,66) = 1.16, p = 0.32, \eta^2 = 0.05$).

Between group comparisons on these recall rates for each recognition test condition showed that participants in the active group recalled significantly more names than the sham group for the faces that were presented in old pairs on the recognition test ($t(22) = 1.78, p < 0.05, d_s = 0.72$) and for the faces that were not presented on the recognition test ($t(22) = 2.30, p < 0.02, d_s = 0.96$), but not for the faces that were presented in lure pairs on the recognition test ($t(22) = 0.59, d_s = 0.21$).

The participants' recall errors were broken into five categories: no response, recalling a name that was never studied, recalling a mis-paired lure name from the recognition test (a source error), recalling a name that was studied with a different face from the same age group, or recalling a name that was studied with a face from a different age group. Participants in the active group failed to enter a name for an average of 38.7% of the trials on the recall test, while the participants in the sham group failed to enter a name for 40.0% of the trials. The difference between the two groups was not significant ($t(22) = 0.19, d_s = 0.08$). Participants in the active group were significantly less likely to enter a name that had never been studied than participants in the sham group (15.6% of trials versus 23.6% of trials, $t(22) = -2.08, p = 0.02, d_s = 0.85$). The

two groups, however, were equally likely to recall names that had been studied with other faces. The participants in the active group entered names that were studied with a different face in the same age group on an average of 9.5% of trials, and names that were studied with a face from a different age group on 7.4% of trials. Participants in the sham group made the same types of errors on 11.3% and 6.0% of trials, respectively ($t(22) = -0.84$, $d_s = 0.33$ for same age group errors and $t(22) = 0.59$, $d_s = 0.18$ for different age group errors). The two groups did not differ significantly in their number of source errors (active 2.5%; sham 1.8%; $t(22) = 0.73$, $d_s = 0.27$). For each of the two groups, **Figure 4** shows the average percentages of blank responses, correct responses, mis-pairings of studied faces and studied names, and instances where participants entered a name that had never been studied. These results indicate that active anodal tDCS improved recall performance while also decreasing some types of errors. Specifically, when participants in the active group entered an incorrect name, it was more likely to be a name that had been studied. Participants in the sham group were more likely to guess a name that had never appeared in the experiment. This pattern supports the idea that active tDCS led to improved recall of the studied names.

As in the recognition test, the participants in the active stimulation group had slightly faster average reaction times than the participants in the sham group (5.4 seconds versus 6.3 seconds), but the difference between the groups was not significant ($t(22) = 1.30$, $p = 0.10$, $d_s = 0.53$).

2.5 Gender Effects

In addition to the overall differences between the active and sham groups, there were differences in recall performance based on the gender of the participants. **Figure 5** shows recall performance broken down by participant gender and face stimulus gender. A 2x2x2 ANOVA

(stimulation condition x participant gender x face stimulus gender) showed that there was a significant main effect of stimulation condition ($F(1,40) = 7.59, p < 0.01, \eta^2 = 0.13$) and a significant main effect of participant gender ($F(1,40) = 11.60, p < 0.01, \eta^2 = 0.19$). Post-hoc t-tests showed that the female participants recalled significantly more names than the male participants in both the sham ($t(10) = 1.83, p < 0.05, d_s = 1.06$) and active conditions ($t(10) = 1.98, p < 0.04, d_s = 1.15$). Interestingly, there were also gender differences in terms of which names participants recalled. Paired t-tests showed that male participants in the sham condition were significantly better at recalling male names than female names ($t(5) = -3.04, p < 0.02, d_z = 1.27$). There was not a significant difference in the ability of the female participants in the sham group to recall male versus female names ($t(5) = 1.21, p = 0.14, d_z = 0.50$). However, numerically speaking, the female participants in the sham condition recalled a higher percentage of female names than of male names, and the lack of statistical significance may be due to the small sample size. In the active stimulation condition, the numeric difference in recall performance for same-gender and opposite-gender names was much smaller for both male and female participants. There were no significant differences in recall of same-gender or opposite-gender names for either male ($t(5) = 0.97$) or female ($t(5) = 0.38$) participants. The same analysis was conducted with the recognition test data, but no significant effects of participant gender were found for that test. A 2x2x2 ANOVA (stimulation condition x participant gender x face stimulus gender) showed no significant main effects or interactions.

2.6 Age Effects

All of the participants in the study were young adults (19-30 years old) while the face stimuli used in the study fell into three age groups: young (ages 19-30), middle-aged (ages 39-55) and old (ages 69-80). For the recognition test accuracy data, a 2x3 ANOVA (stimulation

condition x face stimulus age group) showed a main effect of face stimulus age group ($F(2,66) = 5.40, p < 0.01, \eta^2 = 0.14$) but no main effect of stimulation condition ($F(1,66) = 1.15$).

Participants in both stimulation groups had the best recognition memory for young faces (their own age group) and the poorest recognition memory for old faces.

For the recall test data, a 2x3 ANOVA (stimulation condition x face stimulus age group) showed significant main effects of both face stimulus age group ($F(2,66) = 6.27, p < 0.01, \eta^2 = 0.14$) and stimulation condition ($F(1,66) = 8.47, p < 0.01, \eta^2 = 0.10$). As in the recognition test, participants had the best memory for the young faces and the poorest memory for the old faces. Post-hoc t-tests showed that participants in the active stimulation condition had significantly better recall than participants in the sham condition for young faces ($t(22) = 1.99, p = 0.03, d_s = 0.81$) and for the old faces ($t(22) = 1.89, p = 0.04, d_s = 0.79$), but not for the middle-aged faces ($t(22) = 1.28, p = 0.11, d_s = 0.53$). The recall test performance, broken down by face stimulus age group, is shown in **Figure 6**.

2.7 Perception of tDCS

The participants' average sensation ratings over the course of the experiment are shown in **Figure 7**. Repeated measures ANOVAs (stimulation condition x time) were conducted for each of the sensations recorded on the sensation questionnaires (itching, heat, and tingling). For itching and heat there was a main effect of stimulation condition ($F(1,154) = 16.12, p < 0.01, \eta^2 = 0.31$ and $F(1,154) = 7.91, p = 0.01, \eta^2 = 0.17$, respectively). There was no main effect of stimulation condition for tingling ($F(1,154) = 2.80, p = 0.10$). There was a main effect of time for all three sensations (for itching $F(7,154) = 10.74, p < 0.001, \eta^2 = 0.09$; for heat $F(7,154) = 2.02, p = 0.05, \eta^2 = 0.03$; for tingling $F(7,154) = 8.20, p < 0.001, \eta^2 = 0.15$) as well as a

significant interaction between stimulation condition and time (for itching $F(7,154) = 10.95$, $p < 0.001$, $\eta^2 = 0.08$; for heat $F(7,154) = 3.53$, $p < 0.01$, $\eta^2 = 0.04$; for tingling $F(7,154) = 4.84$, $p < 0.001$, $\eta^2 = 0.09$). To determine if the perception of physical sensations was correlated with performance, we tested the correlations between each participant's average sensation ratings and his or her d_a scores on the recognition memory test and hit rates on the recall test. There were no significant correlations between the sensation ratings and the recognition performance (all $r_s < 0.09$, all $p_s > 0.65$) or recall performance (all $r_s < 0.17$, all $p_s > 0.42$). Consistent with previous work (Clark et al., 2012; Kessler, Turkeltaub, Benson, & Hamilton, 2012), aggregate physical sensations differed significantly between the sham and active stimulation groups, but sensations were not significantly associated with outcome measures. This suggests that the performance differences between groups are indicative of neural modulation rather than nonspecific arousal effects due to physical sensations.

At the conclusion of the experiment session, participants were asked to indicate which level of stimulation they thought they had received. Options read "0.1 mA (sham)," "2.0 mA (active)," and "I was unable to tell." A total of 6 out of 24 participants (3 active, 3 sham) correctly indicated their stimulation condition; the remaining 18 participants (75%) were unable to correctly identify their stimulation condition, which is indicative of successful participant blinding.

3. Discussion

In this experiment, we applied tDCS with the anode positioned above LIFG and measured the resulting effects on memory with both recognition and recall tests. Active stimulation significantly improved participants' recall performance relative to sham stimulation. However, we did not find any evidence of stimulation-based improvements to recognition

performance. These results indicate that tDCS applied during encoding improves associative memory, but that these effects are apparent only when tested under certain retrieval conditions.

Accumulating evidence shows that tDCS improves cognitive performance in healthy adults (Coffman et al., 2014; Manenti et al., 2012). Consistent with prior reports indicating that tDCS can improve performance on recall tests (Boggio et al., 2009, Flöel et al., 2012; Marshall et al., 2004, Penolazzi et al., 2010), we found that stimulation improved recall performance in an associative memory task. Our results indicated that active stimulation substantially improved participants' ability to recall face-name associations. This study used a different type of memory task and stimulated a different brain region than prior studies of recall performance, building a stronger case that anodal stimulation improves memory performance under certain circumstances.

Although the results of the recall test showed that tDCS improved the encoding of the face-name associations, we found no significant effects of stimulation on recognition memory performance. Participants in the active and sham groups did not differ significantly in terms of their hit rates or discrimination performance (d_a). There are several possible explanations for this finding. First, the recognition memory test may be less sensitive to the effects of tDCS. Overall performance was much higher for both groups, so there may not have been enough variability in performance for the effects of tDCS to become apparent. This is consistent with previous work suggesting that the benefit elicited from anodal tDCS may be greater under conditions that are more cognitively demanding (Gill, Shah-Basak, & Hamilton, 2014).

Second, it is possible that the benefits of tDCS to associative memory are most robust after a consolidation interval. Indeed, some evidence suggests that tDCS has both online (e.g., when current is actively being applied; Nitsche & Paulus, 2000) and offline effects on brain

function (e.g., effects that occur after stimulation ceases; Liebetanz et al., 2002), and thus it may be that a sufficient delay is necessary for the off-line effects of tDCS to improve memory. In this study, the recognition test was always completed before the recall test. It is possible that there was a consolidation process that benefited from active tDCS and that the recognition test occurred too soon after study phase to be influenced by that consolidation process. This explanation would be consistent with the findings of Flöel and colleagues (2012), who observed benefits from tDCS on a delayed recall task, but not on a recognition-like incidental learning task that occurred during stimulation. It would also be consistent with the finding that tDCS applied during a consolidation (Marshall et al., 2004) or reconsolidation (Javadi & Cheng, 2013) interval can benefit recall performance. Future work is needed to investigate the interplay of tDCS and consolidation processes on recognition memory performance.

Although speculative, it is possible that tDCS improved memory in this experiment through a strengthening of neuronal connections subserving associative memory performance. Indeed, evidence suggests that tDCS induces LTP-like changes in neurons, which result in the altering of neuronal connections (Liebetanz et al., 2002). Given the nature of associative memory (e.g., learning that this face was paired with that name), it may be that tDCS was effective in promoting cortical connections supporting memory in the active stimulation group. Such a possibility is consistent with prior evidence that a single exposure to tDCS can change connectivity between cortical regions (Hunter et al., 2015).

Recollection refers to retrieval of episodic details regarding the source of information, while familiarity refers to an acontextual sense of having previously experienced a stimulus (Vilberg & Rugg, 2008). Successful recognition may occur as a result of either familiarity or recollection, but successful recall is more likely to involve recollection (Okada, Vilberg, &

Rugg, 2012; Yonelinas, 2002). An examination of the neural correlates of successful recognition and successful recall has suggested the existence of a generic recollection network that supports both recollection-based recognition as well as recall, while familiarity-based recognition is a distinct neural process (Hayama, Vilberg, & Rugg, 2012; Okada et al., 2012). Of relevance to the current study, the hippocampus and adjacent medial temporal lobe (MTL) cortex are thought to play a central role in the recollection network, supporting MTL involvement in episodic memory retrieval (Hayama et al. 2012; Okada et al., 2012).

Given the electrode montage used in the current study, and connectivity between LIFG and temporal lobe structures via the uncinate fasciculus (Jellison et al., 2004), it is possible that selective improvement of recall was due to an effect of stimulation on MTL, downstream from the targeted area. This would suggest that participants were using familiarity-based recognition as a decision basis during the recognition task, while the cued recall portion of the study required a recollection component that was enhanced via stimulation. This is supported by the finding that participants in the active group were significantly less likely to enter an unstudied name during the recall phase of the study. Even when they made errors in terms of recalling which name went with which face, they were more likely than participants in the sham group to recollect a name that had actually been presented during the study phase.

Another possible explanation for our discrepant findings between the recall and recognition results lies in the different ways in which recognition and recall tests assess memory. The two types of tests involve different retrieval processes and may be influenced by memory interventions in different ways (e.g. Payne & Roedigger, 1987). In an associative recognition task, participants can use a recall-to-reject strategy to identify lures. A recognition memory lure essentially provides a participant with two retrieval cues. If the participant can recall the item

that was originally paired with either of these two cues, he or she can reject the lure. This process does not occur on a recall test, where participants must generate the pairing on their own, using only one item as a cue. This difference makes the recognition test easier and may mask improvements in encoding due to tDCS. Indeed, past studies investigating the impact of tDCS on recognition memory have had mixed results, with some studies finding improved performance (Chi et al., 2010; Javadi & Cheng, 2013, Javadi, Cheng, & Walsh, 2012, Javadi & Walsh, 2012) and others finding no improvement on recognition memory tasks (Elmer et al., 2009) or similar incidental learning tasks (Flöel et al., 2012). These results highlight the importance of selecting tests with sufficient sensitivity when testing the effects of tDCS on cognition.

It is also possible that carryover effects of tDCS caused the participants in the active stimulation group to benefit from the recognition memory test in a way that improved their performance on the recall test. The participants in the active group had much higher recall performance for names that were presented in intact pairs on the recognition memory test than participants in the sham group. However, the participants in the active group also had substantially higher recall performance for items that were not presented in the recognition test at all. In addition, if the participants in the active group were recalling more items from the recognition test, we would expect them to have a higher rate of source errors (incorrectly recalling names that were lures on the recognition memory test) than participants in the sham group. The participants made few source errors overall, and the two groups did not differ significantly in terms of their rate of source errors. This pattern of results indicates that the improved memory performance for the active group was probably not driven by improved memory for the items presented in the recognition test.

The gender differences in the recall test raise another intriguing possibility. The sham group findings are consistent with previous demonstrations of an own-gender bias for face recognition (Wright & Sladden, 2003) in that male participants were significantly better at recalling male names than female names. The female participants were numerically better at recalling female names than male names, although this trend did not reach statistical significance. In the active stimulation group, this bias toward recalling more names of the participant's own gender was absent and there were no significant differences in rates of recalling male and female names for either male or female participants. This pattern could indicate that participants find it more difficult to recall the names of people of the opposite gender, and that tDCS provides a bigger benefit to the memory conditions that are more difficult. Recognition is easier than recall, so the benefits of tDCS were not apparent on that less challenging task. On the difficult recall test, tDCS had a significant impact on performance, and had the most impact on the items that would otherwise have been the most difficult for the participants to recall. This is an interesting possibility, but future research will be needed to tease apart the reasons for the gender-related differences seen in this study.

Face-name pairs were selected as stimuli in part because of their real-world relevance. Previous research has demonstrated that elderly participants perform significantly worse than young adults on both recognition and recall of names associated with faces, and those with Alzheimer's disease perform significantly worse than their healthy age-matched counterparts (Sperling et al., 2003a). The same study reports significantly less activation in inferior prefrontal cortices for elderly individuals during encoding of face-name pairs (Sperling et al., 2003a). This decreased activation is perhaps related to the performance decrement, since Sperling and colleagues have separately demonstrated LIFG activity to be predictive of face-name pair

encoding (Sperling et al., 2003b). Patients with Alzheimer's typically experience significant associative memory impairment early in the course of the disease (Fowler et al., 2002) and difficulty with remembering proper names has been identified as the most common complaint voiced by elderly individuals visiting memory clinics (Leirer, Morrow, Sheikh, & Pariente, 1990). Recently, tDCS applied bilaterally over the temporal cortex has been used to effectively enhance visual recognition memory for participants with Alzheimer's (Boggio et al., 2012). Additionally, tDCS has been used to enhance episodic memory and reduce forgetting in healthy elderly participants (Sandrini et al., 2014) with one study eliciting improvement with left hemisphere stimulation only (Manenti et al., 2013). Based on the success of the current study in improving name recall by targeting LIFG and prior success regarding tDCS enhancement of episodic memory for elderly individuals, treatment of face-name memory deficit via targeted stimulation of LIFG seems an avenue worth exploring.

Overall, the results of this study suggest that associative memory is improved by anodal tDCS administered during encoding, but that the memory improvement is only evident under some testing conditions. These results add to the growing body of literature indicating that tDCS can enhance various aspects of cognitive performance in healthy adults. They also point to some intriguing avenues for future research, including gender differences in memory and response to tDCS, and the impact of tDCS on memory consolidation. These data raise the possibility that tDCS has the biggest benefit to memory on the tasks that are the most difficult for participants. Our findings add to the growing body of literature that tDCS is an effective intervention for improving cognitive function in healthy adults.

4. Methods and Materials

4.1 Participants

Twenty-six student interns at Sandia National Laboratories, 13 male and 13 female, participated in the study after giving written informed consent. All participants were right handed as measured by the Edinburgh handedness inventory (Oldfield, 1971), native English speakers with no history of neurological or psychiatric disorders, head injuries, or vision or hearing problems. None of the participants had surgical or other metal implants in their head, neck, shoulders, or arms, and none reported taking any psychoactive medications at the time of the study. In addition, participants were excluded if they had prior exposure to tDCS. Half of the participants were assigned to the active stimulation group and half were assigned to the sham stimulation group in a double-blind design. Two of the participants (one male and one female) were excluded from data analysis due to failure to follow task instructions, resulting in a total of 12 participants (6 male and 6 female, average age 22.25, SD = 3.04, range 19-30) in each of the tDCS conditions. No significant differences in age, handedness quotient, or years of education were present between tDCS groups, as determined by individual independent-samples t-tests with $\alpha = 0.05$.

4.2 Materials

The images used in this study were drawn from the neutral emotion photographs in the FACES database (Ebner, Riediger & Lindenberger, 2010). The people in the photographs ranged in age from 19 to 80 and a plausible first name was assigned to each individual. The names were drawn from the Social Security Administration's lists of the most common names from each decade (e.g., 1930s-1990s). Based on the age and gender of each person in the images, a name was selected from among the 60 most common names of the decade in which that person was born. Names that have been popular for both males and females (such as Taylor) were excluded,

and care was taken to include only one variant of names that have several popular versions or very similar sounds (e.g. Richard/Rick, or Gene/Jean). Nine face-name pairs were used for the practice session, 36 pairs were used for a baseline memory test prior to stimulation, and 108 pairs were used for the main associative memory task. For the 108 pairs used for the main task, the face-name pairs contained equal numbers of males and females and equal numbers of faces from each age group. This included 18 young women, 18 young men, 18 middle aged women, 18 middle aged men, 18 older women and 18 older men.

Two questionnaires were developed to assess the participants' physical sensations in response to tDCS and to assess any impact of the stimulation on the participants' mood. In the sensation questionnaire, participants were asked to use an 11-point Likert scale ranging from 0 ("none") to 10 ("excessive") to report their perception of each of three sensations – tingling, itching, and heat/burning. The sensation questionnaire was administered eight times during stimulation, first at one minute after the onset of stimulation and again every four minutes for the duration of the stimulation. In the mood questionnaire, participants were prompted to indicate their level of agreement with 10 statements, such as "I feel nervous" and "I feel unable to concentrate or pay attention" on a six point Likert scale, ranging from 0 ("not at all") to 5 ("very much"). This questionnaire was included because previous research has indicated that stimulation near regions homologous to those targeted in this study may impact mood and affect (Barrett et al., 2004). While the specific stimulation parameters in this study are somewhat different (e.g., along the dimensions of current strength, electrode size, and exact electrode location) from those used in studies that have found mood effects, we collected mood data via the questionnaire before and after stimulation to document any changes.

4.3 Procedure

The structure of the experiment is shown in **Figure 1**. Before starting the experiment, participants gave their informed consent, were screened with the inclusion and exclusion criteria, and provided demographic and handedness information via paper questionnaires. Participants then completed a mood questionnaire to serve as a baseline. The associative memory task was presented using E-Prime software and consisted of three phases. First, participants were given an overview of the memory task and instructions for the study phase, recognition test, and recall test (described in more detail below). They completed a practice session in which they studied nine face-name pairs and completed recognition and recall tests for those pairs. In the second phase, participants completed a baseline memory test in which they studied 36 face-name pairs and completed the recognition and recall tests. The baseline test was a shorter version of the main experimental task and was used to compare the active and sham groups to determine whether or not there were any performance differences between the two groups prior to stimulation. Then the electrodes were placed on the participant immediately before the third phase, in which participants completed the main associative memory task. Following initiation of stimulation, participants periodically reported physical sensations in tandem with the main task. In the main task, participants studied 108 face-name pairs (different from the pairs studied during the practice and baseline phases) while receiving either active or sham stimulation. Following stimulation, participants completed the recognition and recall tests.

During the study phase, a picture appeared in the center of the computer screen with a name directly below it. Each face-name pair stayed on the screen for seven seconds. Participants were asked to study each face while it was on the screen and to try to memorize that person's name. After each face-name pair disappeared, the participants were given two seconds to answer whether the name "fit" the face (yes/no). This face-name study task (does the name fit the face?)

was based on the task used by Sperling and colleagues (2003b). During tDCS, all participants studied the same list, which consisted of 108 face-name pairs. The pairs were presented in a pseudorandom order with no more than four faces of the same gender or age group appearing consecutively. Study trials were divided into six blocks containing 18 pairs each. After each study block, participants took a short break and filled out the sensation questionnaire. The study session ended approximately five minutes before the end of stimulation. Following cessation of stimulation, electrodes were removed and participants began the recognition test.

In the recognition memory test, participants were again shown face-name pairs, half of which were correct pairings and half of which were recombined pairs in which a previously studied picture was paired with a name that had been studied with a picture of a different person of the same gender and age group. Below the face-name pair, participants saw the question “Is this the correct name?” They responded using a 1-4 scale, with “1” indicating that they were sure it was the correct name, “2” indicating that they thought it was the correct name, but were unsure, “3” indicating that they thought it was the *not* correct name, and “4” indicating that they were sure it was *not* the correct name. Each face-name pair remained on the screen until the participant responded with a key press. Participants saw one of three counterbalanced test lists that contained 36 old face-name pairs and 36 recombined face-name pairs. The pairs were counterbalanced across lists so that the items were tested equally often in old and recombined pairs.²

² For example, all participants studied the pairs FaceA-NameA, FaceB-NameB, and FaceC-NameC at study, where FaceA, FaceB and FaceC were all people of the same gender and age group. One-third of the participants were then tested on the pairs FaceA-NameA (old) and FaceB-NameC (recombined), one-third were tested on the pairs FaceB-NameB (old) and FaceC-NameA (recombined), and one-third were tested on the pairs FaceC-NameC (old) and FaceA-NameB (recombined).

Immediately following the recognition test, participants were given a recall test. In the recall test, participants were shown faces from the study list, one at a time, and were asked to type in each person's name. They were encouraged to guess if they could not remember the name or to type "no" if they did not have a guess. Each face stayed on the screen until the participant typed his or her response and hit the "enter" key. Misspelled names were counted as correct. Participants saw 72 faces that were studied in the study session and were asked to type in each person's name. Of those faces, 24 had been tested as old pairs in the recognition memory test, 24 had been tested as part of recombined pairs in the recognition test, and 24 were not used in the recognition memory test (these were the studied faces whose names were re-paired with different faces to create the lures on the recognition memory test). Across participants, each face fell into each of these conditions an equal number of times.

At the end of the experiment session, participants were asked to guess whether they were in the active or sham condition and give reasons for their guess. They also completed a questionnaire describing any memory strategies that they used to complete the task.

tDCS Procedure

tDCS was delivered using an ActivaTek ActivaDose II system. The electrode locations were first swabbed with an alcohol pad. In order to avoid bias arising from positioning electrodes with opposite polarity cephalically, we used an extracephalic reference electrode. The cathode was placed on the upper right arm of the participant, on a fleshy area near the bicep between the elbow and the shoulder, and then the anode was placed over the left sphenoid bone, near location F9 on the international 10-20 EEG system, above the left inferior frontal cortex. Current was delivered for 30 minutes at either 0.1mA (sham) or 2.0mA (active) via 3cm x 3cm (11cm²) sponge electrodes saturated with saline (6.25mL of 150mM concentration NaCl solution per

sponge) and secured to the participant using Coban self-adhering wrap. Immediately prior to stimulation impedance was measured for each participant (average impedance 59.38 kOhms, SD = 18.43, range 14-78).

A current strength of 0.1mA was chosen as the sham stimulation condition in order to induce physical sensations typically associated with tDCS without stimulating the cortical area beneath the anodal electrode. Indeed, current modeling studies suggest that current strength less than 0.5mA at the electrode size used in this experiment have no impact on brain activity in neural tissue 12mm beneath the surface of the skin (Miranda, Faria, & Hallett, 2009). In our sham condition, participants received 20% of this current strength, making it unlikely that the 0.1mA administered would have a meaningful impact on brain function. Further, we chose this sham procedure because the traditional method of ramping up the current at the initiation of stimulation then ramping it back down (typically after 30s) may not be effective in blinding participants to stimulation condition, given that sensations associated with active stimulation persist beyond this 30s window (Dundas, Thickbroom, & Mastaglia, 2007; Poreisz, Boros, Antal, & Paulus, 2007).

Double-blinding was accomplished via a switch box designed to deliver active or sham stimulation based on coded assignment made by a third party, identical to the blinding procedure described elsewhere (Coffman, Trumbo, & Clark, 2012). The blinding and sham methodology used in this study was identical to that used effectively in several prior studies (Coffman et al., 2012; Falcone, Coffman, Clark, & Parasuraman, 2012). Coding was released to the experimenters following completion of data collection.

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Figure Captions

Figure 1. Overview of study design.

Figure 2. Average proportion of each response type for the old and recombined pairs tested on the recognition test.

Figure 3. Average proportion of names recalled correctly by the active and sham groups. A: Overall proportion of names recalled by the active and sham groups. B: Average proportion of names recalled for each of the recognition memory test conditions.

Figure 4. Average percentages of correct, unstudied, and mis-paired names entered on the recall test by the active and sham groups.

Figure 5. Comparison of average hit rates for male and female participants in the active and sham groups recalling the names of male and female faces.

Figure 6. Average proportion correct on the recall memory test for face-name pairs from different age groups.

Figure 7. Average sensation ratings for the participants in the active and sham groups for each of three sensations (itching, heat, and tingling) at eight points during tDCS stimulation.

Figure 1

Figure 2

Figure 3

(A)

(B)

Figure 4

Figure 5

Figure 6

Figure 7