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EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON CATEGORY LEARNING IN OLDER ADULTS

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by

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DISSERTATION

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ABSTRACT

Those over the age of 65 occupy a growing proportion of the population. With this growth, cognitive issues that accompany aging are increasingly coming to the forefront, yet despite this focus, ways to ameliorate cognitive issues in older adults are lacking. Transcranial direct current stimulation (tDCS) offers one possibility for improving cognitive function in older adults, but tDCS application is hindered by individual factors that manifest as heterogeneity in outcomes across the literature. This is especially the case in older adults, where changes in anatomy and functionality provide a potential complication for tDCS application. Presented here are three studies seeking to explicate some of that heterogeneity. In Study 1, the behavioral effects of tDCS in older adults are delineated, specifically whether those with and without Mild Cognitive Impairment experience different effects. In healthy older adults, there was a main effect of active tDCS on task performance where accuracy was increased across all blocks. In those with MCI, an interaction between active tDCS and task block was observed, such that improvement in the task did not occur until after 20 minutes. In Study 2, finite element modeling of tDCS current flow was performed in order to understand how changes in white matter, grey matter, and cerebrospinal fluid impact the current introduced by tDCS. Among those who received active tDCS, significant relationships existed between white matter and cerebrospinal fluid ratios and task performance, with higher white matter

and lower cerebrospinal fluid ratios predicting better performance in the active tDCS group. Lastly, higher electric field magnitude underneath the electrode was predictive of better task performance in the active stimulation group. In Study 3, differences in resting state functional connectivity at baseline were used to predict benefit following active tDCS. Consistent with findings of dedifferentiation in older adults, where functional connectivity patterns in older adults are less segregated than those in younger adults, stronger intraconnectivity in the front-parietal control network was predictive of better task performance in those who received active tDCS. Together, these results highlight how brain differences in older adults can affect tDCS application, and how understanding these differences can ensure that the potential benefits of tDCS in older adults are maximized.

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Abstract

The number of adults over the age of 65 is increasing, but the common cognitive disorders that affect older adults are inadequately addressed. Transcranial direct current stimulation (tDCS) is an emerging technology that could play a role in improving cognition in older adults. In a randomized, sham-controlled study, tDCS was applied to the right inferior frontal gyrus of 82 adults between the ages of 50 and 84 with and without Mild Cognitive Impairment. TDCS was applied once (2 mA for 30 minutes) during the training portion of a visual categorization task featuring discovery learning. In healthy older adults, there was a main effect of active tDCS on accuracy where accuracy was increased across all the blocks. In those with MCI, an interaction between active tDCS and task block was observed, such that improvement in the task did not occur until after 20 minutes. An increase in reaction time with active stimulation was also observed in the healthy control group. These findings offer promise for future tDCS work in both healthy older adults and those with cognitive impairment. However, the current study provides evidence that differential effects occur between these groups and future studies should seek to elucidate the differences that underlie these contrasting effects.

Introduction

The proportion of older adults in the population is increasing. In the United States, it is forecasted that the population of adults over the age of 65 will increase from around 55 million in the year 2022 to nearly 85 million by the year 2050 (Ortman, 2014). Those over the age of 65 are also living longer, with the average life expectancy of a 65 year old increasing from 15 to 19 years since the 1970's (Ortman, 2014). With an aging population, awareness of possible cognitive issues associated with aging is becoming increasingly widespread, leading many older adults experiencing changes in their subjective cognitive function to seek medical consultation (Jessen et al., 2020). A third of adults over the age of 65 are affected by some form of diagnosable neurocognitive decline (DeCarli, 2003), but even those who do not meet the criteria for cognitive disorders associated with aging, such as Alzheimer's and Mild Cognitive Impairment (MCI), still report subjective changes in cognitive function that can be distressing (Harada et al., 2013; Jessen et al., 2020). An increasing population of older adults, coupled with an increasing awareness of the deleterious effects of cognitive decline, will likely increase the costs associated with treating age-related cognitive problems in the future, which already worldwide is estimated at a trillion dollars per year (Patterson, 2018). Despite this financial outlay and an increasing awareness, current interventions to alleviate neurocognitive decline are largely ineffective (Fink et al., 2018; Kane et al., 2017), meaning that better methods for combating neurocognitive decline are needed.

One possible method for combating neurocognitive decline is a form of noninvasive brain stimulation, transcranial direct current stimulation (tDCS), which holds several key

advantageous features. Compared to other interventions, tDCS is inexpensive and easy to implement, so could potentially be used as a preventative measure in older adults not yet experiencing cognitive decline, or as an intervention in those who have been diagnosed. In tDCS, small electrodes are placed on the scalp and these deliver a weak current typically in the range of 1 to 2 milliamps (mA). The electrical currents induced by tDCS, after passing through the skull and into the brain, are able to modulate the potential of neuronal membranes, change synaptic function (Liebetanz et al., 2002; Nitsche & Paulus, 2000, 2001), and then possibly change cognitive function. In a population of neurons, anodal stimulation, where the current flows into the brain, generally induces a depolarization of neuronal membranes that makes action potentials more likely, while cathodal stimulation, where the current flows out of the brain, produces a polarization that makes action potentials less likely (Lefaucheur et al., 2017; Nitsche et al., 2003). However, this is a net effect and individual neurons underneath the electrode may respond differently according to their orientation or shape. Indeed, all neurons are simultaneously hyperpolarized and hypopolarized, such that in a typical neuron, with its long axis reaching towards the anodal electrode at one end and the soma reaching away from the anodal electrode at the other end, the dendrites at the end of the long axis will be hyperpolarized while the soma is depolarized (Bikson et al., 2004). In cases where the neuron is at any orientation between 89 and 144 degrees to the anodal electrode, any excitation effect will be weaker, while an inhibitory effect would be observed if the neuron was oriented between 146 and 180 degrees relative to the anodal electrode. For cases when the neuron is perfectly perpendicular to the current flow, or the shape of the neuron itself is symmetrical, then the effect of tDCS current on excitability would be null (Rawji et al., 2018). In the idealized case of an asymmetric neuron at 90 degrees to the anode, the

maximum theorized change to membrane potential is between 0.2 and 0.5 mV, accounting for at most 2.5% of the change needed to get a resting neuron to firing threshold (Opitz, Falchier, Yan, Yeagle, Linn, Megevand, Thielscher, A, et al., 2016; Radman et al., 2009). This means that any effect on behavior tDCS might have is one where this small physiological effect is compounded across an entire network of neurons. In practice this means that, 1) sound experimental design is vitally important to ensure that the small effect of tDCS is maximized, and 2) that individual differences are quite capable of nullifying any benefit of tDCS.

One protocol that has previously been shown to maximize the effects of tDCS is anodal application to the right inferior frontal gyrus (rIFG; or F10 in the 10-20 EEG system) coupled with the cathode placed on the left arm. Applied concurrently during learning (i.e. "online" stimulation), this protocol has demonstrated beneficial effects on performance with effect sizes up to $d = 1.2$ (Clark et al., 2012; Coffman et al., 2012; Falcone et al., 2012), more than double the effect size found in a meta-analysis for tDCS applied during learning across various protocols (Simonsmeier et al., 2018). The initial studies of the F10 protocol were conducted in a training task called DARWARS where subjects are tasked with learning to identify threats in computer generated pictures of urban areas of the Middle East (Clark et al., 2012; MacMillan et al., 2005). Subsequent research has used the Predicting Response To F10(X) tDCS (PRETXT) task (Gibson et al., 2020, 2021). In this task, pictures of European streets are presented one at a time on a computer screen and subjects are instructed to learn the arbitrary rules that separate the pictures into two categories. These tasks are different but have important similarities: both require sustained attention and discovery learning,

processes that are both associated with the rIFG stimulation site through both stimulation and imaging findings (Mayseless & Shamay-Tsoory, 2015; McKinley et al., 2013; Nelson et al., 2014; Seger et al., 2000; Seger & Cincotta, 2006).

While the F10 tDCS protocol has been previously successful in improving performance in the PRETXT task, that was in a sample of young adults with an average age of 23.2 (*SD* = 8.34) (Gibson et al., 2020). For older adults, changes in cognition and brain structure provide potential complications for tDCS application. Across the literature, tDCS has been applied to both older adults with cognitive impairments and to healthy older adults using a variety of experimental parameters (Chen et al., 2022; Indahlastari, Hardcastle, et al., 2021a). Working memory has been a common target for tDCS in healthy older adults. The majority of these studies have been successful in improving measures of working memory, with a systematic review noting that 10 of 14 studies reported improvement (Goldthorpe et al., 2020). In another recent meta-analysis (Indahlastari, Hardcastle, et al., 2021a), the effect size for tDCS across cognitive studies in healthy adults over 65 was a moderate $g = 0.63$. The reviewed studies all applied tDCS to the frontal cortex to improve attention ($g = 0.63$), working memory ($g = 0.48$), error awareness ($g = 0.54$), and episodic memory ($g = 1.2$) (Indahlastari, Hardcastle, et al., 2021a). Some of the reviewed working memory studies applied tDCS over multiple days, ranging from 5 sessions to 20, but all studies exploring other cognitive abilities applied a singular session of tDCS. Interestingly, there was no difference in effect size within the working memory domain between studies applying tDCS once ($g = 0.51$) and studies applying tDCS on multiple occasions ($g = 0.51$) (Indahlastari, Hardcastle, et al., 2021a). Across cognitive processes there is evidence that single session tDCS is capable of

improving functions in healthy older adults, but there is no clear evidence to support a specific stimulation length or strength (Indahlastari, Hardcastle, et al., 2021a).

Compared to the above findings in healthy older adults, evidence for tDCS improving outcomes in those with MCI or Alzheimer's is mixed to poor (Chen et al., 2022; Inagawa et al., 2019; Rajji, 2019). Across numerous outcomes in a recent meta-analysis, including recognition memory, attention, and executive function, tDCS application failed to benefit those diagnosed with Alzheimer's or MCI. An exception to this pattern was the mini-mental state examination, which was included in 11 of 16 reviewed studies and showed a small average improvement across studies (Chen et al., 2022). However, in this body of studies only 1 applied online tDCS, while the rest applied offline tDCS across multiple days ranging from 3 sessions per week for 2 weeks to daily sessions for 6 months (Ferrucci et al., 2008; Im et al., 2019). While a greater number of sessions was found to elicit a greater benefit across studies, the paucity of previous research exploring online application of tDCS in those with MCI leaves open the possibility that even single session online stimulation could be effective. An important difference in comparing studies conducted in healthy older adults and studies conducted with those with MCI is that, while the majority of studies in healthy older adults applied online stimulation, the opposite was true of studies with MCI, where the majority are offline. It is thus possible that online stimulation could have better results than those seen in meta-analysis, even if those few studies applying online tDCS across multiple sessions have not found consistent benefit (Cotelli et al., 2014; Inagawa et al., 2019).

While existing work applying tDCS to both healthy older adults and those with MCI shows some promise, those parameters that maximize the effects of tDCS in these populations has yet to be discovered. The goal of the current study was to improve performance on the PRETXT task by applying the previously successful F10 protocol to a sample of older adults, both those considered healthy and those with MCI.

Methods

Subjects

Both healthy older adults and those with MCI were recruited for this study from the Albuquerque, New Mexico, area. All data collection occurred at the Mind Research Network. MCI status was determined either by prior diagnosis by a medical professional, as reported by the subject themselves or a subject's caregiver, or by an assessment conducted as part of the study. For this study we classified both subjects with a preexisting diagnosis of MCI, and those without a diagnosis of MCI but who scored a 25 or lower on the Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005a), as having MCI. The inclusion criteria for healthy controls in the study were as follows, 50-90 years old, right handed, learned English by age 7, no history of psychiatric hospitalization or current psychosis, no excessive drug, alcohol or nicotine use, no significant history of epilepsy, migraines, stroke or traumatic brain injury, no neurodevelopmental disorders such as ADHD, not taking medications with significant psychotropic effect, no severe sensory impairment, no severe chronic illnesses, not requiring a helper animal, no previous experience with tDCS, no metal or electronic implants that might interfere with stimulation or be an magnetic resonance imaging (MRI) contraindication, no allergies to nickel or latex, no current potential COVID-19 symptoms.

For subjects with MCI, inclusion criteria were identical expect for exceptions concerning medications with psychotropic effects, where medications related to neurodegenerative condition and medications for anxiety and depression were allowed. MCI patients also needed to be able to sign a consent form, or have a legally authorized representative able to sign on their behalf. In order to ensure understanding of the consent form, subjects were asked a series of questions about information presented in the consent form such as, “Tell me the main risks and possible benefits of participating in this study”. Subjects were paid $10 dollars per hour as well as receiving bonuses for completing specific portions of the study, including $25 for the MRI, $25 for a blood draw and $10 dollars for completing all portions of the study. Prior to the beginning of the study, it was anticipated that some individuals would complete the MRI, while others would not due to preference, contraindications to MRI, or funding constraints.

Upon arrival at the Mind Research Network, all subjects were informed of the details and goals of the study, including the use of tDCS and MRI, and consented. For those who received an MRI, participation lasted 6-8 hours spread over two days (Figure 1). On day 1 subjects completed 2-3 hours of neuropsychological assessment including the MOCA, followed by their first MRI scan, with the MRI scan lasting around 1.5 hours. During this scan subjects completed several measures, including structural, resting state, and the baseline portion of the PRETXT task. On day 2 subjects completed the training portion of the PRETXT task while receiving tDCS. Immediately after the training portion was complete, subjects returned to the scanner and completed the test portion of the PRETXT task in addition to other measures. For subjects who did not receive an MRI, participation lasted 4-6

hours and was also spread over 2 days. On day 1 subjects completed the same neuropsychological assessments. Then on day 2 subjects completed all portions of the PRETXT task consecutively (Figure 2).

PRETXT Task

The experimental task was a modified version of that used previously (Gibson et al., 2020, 2021), created and presented in E-Prime Version 3 (Psychology Software Tools, Sharpsburg, PA). The goal of the PRETXT task is to learn to correctly classify pictures of European streets into 2 categories. All pictures were standardized to be 1,670 pixels wide and between 600 and 750 pixels tall when presented on a computer monitor with a display resolution of 1920 by 1080. In centimeters these dimensions were 52 by 19-24. When presented in the scanner on a JVC DLA Multimedia projector (Model DLA-SX 200), the dimensions of the picture were 30 cm by 22 cm. Participants were much closer to the image in the scanner, a distance of 14 cm compared to 85 cm outside, meaning that horizontal and vertical visual angles were larger inside the scanner, 93 by 76 degrees, compared to outside, 34 by 16 degrees. Within the scanner, responses were recorded using a MIND Input Device (https://www.mrn.org/collaborate/mind-input-device), and outside using a computer keyboard. The task was broken into 3 segments, baseline, training, and test. Throughout the task, static street views were presented on the screen for 2.5 seconds. During those 2.5 seconds subjects needed to respond with a button press saying whether they thought the picture belonged in category 1 or 2. Following 2 baseline blocks of 50 trials without feedback, there were four blocks of training, each with 60 trials in which subjects received accuracy feedback following each response telling them if they had correctly categorized the

previous picture. Accuracy feedback consisted of a screen stating that subjects either responded correctly, incorrectly, or failed to respond in the 2.5 second interval. This written feedback was accompanied by corresponding auditory feedback consisting of male voices with various European accents. Training blocks were followed by the post-test, which like the baseline did not have feedback. The test blocks consisted of four blocks of 50 trials each. The baseline set was framed as a practice block during which subjects were instructed to become accustomed to the timing of the stimuli and to begin hypothesizing about criteria that might differentiate the categories.

To successfully perform the task, subjects needed to learn that an arbitrary difference separated the 2 categories, specifically that pictures taken on the left-hand side of the road where traffic would be approaching them belonged to category 1, while pictures taken on the right hand side where traffic would be moving away belonged to category 2. Prior to beginning the study, subjects were only told that there were two categories and were not informed about any possible ways to differentiate them. Instead, through discovery learning (Bruner, 1961), they were tasked with gaining knowledge of the pertinent criteria via feedback during the training portion. For those who completed the baseline, training, and test sections of the task outside of the MRI, the baseline and test sections were performed on the same desktop computer on which all subjects completed the tDCS-accompanied training portion. After completion, subjects were asked what they thought was the critical difference or differences between category 1 and 2, and to list the criteria they tried through the training portion in order to try and correctly classify the pictures. For all blocks of the PRETXT task,

accuracy was calculated by dividing number of trials correct by total number responses. Trials in which the subject did not respond in time were not counted.

tDCS

TDCS was administered via an ActivaDose II iontophoresis unit (Activa Tek, Inc.). Double blinding was performed using a blinding box displaying 6 switches. Two ActivaDose II units were connected to the blinding box, one delivering the active dose and one the sham dose, and specific switches on the blinding box allowed the current of one or the other of the machines to pass. Subjects were randomized to receive an active anodal dose of 2.0 mA or a sham dose applied to F10, with the return cathodal electrode placed on the contralateral triceps. Subjects were randomized to a switch associated with one of these conditions beforehand and the researcher administering tDCS was unaware of the dosages associated with the 6 switches. Two 5x5 cm sponges with a metal backing enclosed in a rubber holder were used to deliver tDCS current. Sponges were soaked overnight in SignaGel electrode paste. The electrode was attached to the subject's head with an Amrex Velcro strap and to the arm with Coban adhesive wrap. Stimulation lasted 30 minutes and began after the baseline block. At 30 seconds and 4 minutes after the beginning of stimulation, subjects completed a sensation questionnaire asking them to rate the degree of itching, heat, and tingling on a 0-10 Likert-type scale. Subjects were informed that sensations rated 7 or above would prompt the termination of stimulation and end the experiment. After the first five minutes of stimulation, subjects began the 1st training block, with stimulation ending in the last minute of the 3rd training block. Following completion of the training portion, subjects were asked to guess whether they believed they received real or placebo stimulation.

Statistical Analysis

Analyses were conducted in Statistical Product and Service Solutions (SPSS) and R. To understand differences in accuracy and reaction time between tDCS conditions, linear mixed models (LMM) were used. LMM were created using the R package lme4 (Bates et al., 2014). LMM are superior to repeated measures analysis of variance (ANOVA) for the current analysis because they are better able to account for the violation of sphericity and able to include subjects with missing data. LMM also account for nested observations, time within people, and correlated residuals between people across the 9 blocks. Three different models for accuracy and reaction time were constructed. In both cases there was a combined model with both HC and MCI subjects, as well as models for each group separately. The models for accuracy included main effects of tDCS condition and block (baseline thru test, 1-9, with the 2 baseline blocks combined) and the interaction between block and condition. Blocks 1-9 were coded -4 to positive 4 so that the main effect of condition represented the impact on accuracy averaged over all blocks. Those for reaction time additionally included accuracy (grand-mean centered) to explore whether reaction time was changed across stimulation conditions regardless of accuracy. All models included random intercepts and slopes and used restricted maximum likelihood. Additional analyses were performed in SPSS. These included one-way ANOVAs examining possible differences in sensations between stimulation groups and cross-tabulation and χ^2 test to examine possible differences in other between-groups variables including sex and guessed condition (active stimulation or placebo stimulation).

Hypotheses

1) Healthy control subjects who receive active stimulation will demonstrate greater rule learning (as measured by increased in categorization accuracy during training and test relative to baseline) compared to subjects who receive sham stimulation.

2) Subjects with MCI/AD who receive active stimulation will demonstrate greater rule learning (as measured by categorization accuracy during training and test relative to baseline) compared to subjects who receive sham stimulation.

Results

Data from 82 subjects was collected for the analyses, with 25 subjects classified as MCI and 57 as healthy controls (Table 1). The average age for the entire sample was 66.9 (*SD* = 9.1) and ranged from 50 to 84. The average was 63.9 (*SD* = 7.3) for the HC group and 73.8 (*SD* = 8.9) for those with MCI. Out of the entire sample of 82, 37 subjects or 45% were male. Broken down by group it was 19 out of 57 or 33% male in the HC group, and 18 out of 25 or 72% male in the MCI group. The distribution of sex and diagnosis was such that there was a significant relationship between them, χ^2 (1, N = 82) = 10.49, p = 0.001), with those in the MCI more likely to be male (72%) and those in the HC group more likely to be female (67%). Out of the total sample, 2 participants classified themselves as Native American and both were healthy controls. Two participants classified themselves as black, with one being a HC and one being classified as MCI. Seventeen individuals classified themselves as Hispanic, with 5 of these considered as MCI participants for this study. The rest of the sample of 61 classified themselves as white, which included 19 participants with MCI.

Overall, 43 (13 MCI) of the final sample received active stimulation and 39 (10 MCI) received the sham dose. Twenty-nine (9 MCI) subjects who received active stimulation and 29 (8 MCI) who received sham performed the baseline and test blocks in the scanner while 14 (4 MCI) in the active group and 10 (4 MCI) in the sham group performed these parts of the study outside the scanner. One-way ANOVAs indicated significant differences in sensations between groups (Figure 3). While there was no significant difference in heat at time 1 ($F(1,80) = 1.45$, $p = 0.232$) or time 2 ($F(1,80) = 0.087$, $p = 0.769$), ($F(1,80)$, itching and tingling were significantly different at time 1 ($F(1,80) = 11.16$, $p = 0.001$), ($F(1,80) = 13.57$, $p < .001$) and time 2 ($F(1,80) = 8.12$, $p = 0.005$), ($F(1,80) = 10.69$, $p = .002$). At both of these time points those in the active group reported greater itching (time 1: $M = 2.65$, $SD = 1.9$; time 2: $M = 2.16$, $SD = 1.36$) and tingling (time 1: $M = 2.42$, $SD = 1.24$; time 2: $M = 2.19$, $SD = 1.2$) compared to the sham group (itching at time 1: $M = 1.54$, $SD = 0.88$; time 2: $M = 1.44$, $SD = 0.85$) (tingling at time 1: $M = 1.56$, $SD = 0.78$; time 2: $M = 1.44$, $SD = 0.82$). Despite this there was no significant relationship between assigned condition and guessed condition with the possible guesses being active, placebo, and unsure χ^2 (2, N = 82) = 2.86, $p = 0.239$).

Linear Mixed Models

For both accuracy and reaction time, there were 718 observations from 82 subjects. Test data from 5 subjects tested in the scanner, 1 active and 4 sham, were missing. These 20 missing observations were estimated with restricted maximum likelihood conditioning on all model predictors and weighing those with complete data sets more heavily. In examining the data prior to analysis, it was observed that there were differences in accuracy and reaction time

between those who performed the baseline and test in the scanner and those who performed these blocks outside the scanner. Whether a subject was part of the MRI portion of the study was thus added as a covariate to the models and coded .5 or -.5.

Accuracy

The intraclass correlations (ICC) for the combined, HC, and MCI models differed. The combined group ICC was 58%, meaning that 58% of the variance in accuracy was due to between-person differences, while 42% was due to change over time. The ICC in the HC was similar to that of the combined group at 60%. However, the ICC for the MCI group was 40%. In the total sample (Figure 4; Table 2), the main effect of active stimulation on categorization accuracy was not significant across all blocks (b(SE) = 3.07(1.68), p = 0.072). The interaction between block and tDCS condition was also not significant (b(SE) = 0.62(0.44), p = 0.164), and the model examining the interaction between block and condition did not fit significantly better than model with main effects only ($\chi^2(1) = 2.01$, p = 0.157). For the HC group only (Figure 5; Table 3), the main effect of active stimulation was significant (b(SE) = 4.78(1.94), p = 0.017), meaning that active stimulation cohort exhibited greater categorization accuracy averaged across all blocks compared to sham. The interaction between block and condition was not significant, (b(SE) = 0.3(0.58), p = 0.607), and as in the combined sample, the model including the interaction between block and condition did not significantly improve model fit ($\chi^2(1) = 0.28$, p = 0.599). In the MCI group (Figure 6; Table 4), the main effect of tDCS condition was not significant (b(SE) =2 .59(2.88), p = 0.377). However, the interaction between condition and block was significant (b(SE)=0.6(1.17), p =

0.032). Accordingly, the model including the interaction between block and condition had significantly better fit than the main effects only model ($\chi^2(1) = 5.23$, $p = 0.022$).

Reaction Time

The ICCs for reaction time were similar: 37% for the combined group, 39% for the healthy control group, and 30% for the MCI group. For the combined sample (Figure 7; Table 5), the main effect of accuracy was significant (*b*(SE) = -3.72(0.88), $p < 0.001$, where increased accuracy was associated with decreased reaction times. The main effect of tDCS condition on reaction time was not significant (*b*(SE) = -40.51(36.4), $p = 0.269$), nor was the interaction between block and condition (*b*(SE) = -9.41(8.71), $p = 0.283$). The main effect of whether an individual subject performed the baseline and test blocks in the MRI was also significant, with those in the MRI having a significantly faster reaction time in milliseconds (*b*(SE) = -117.17(39.67), $p = 0.004$) (Figure 8; Table 5). Examining the HC group alone, the main effect of accuracy was again significant, (*b*(SE) = -4.12(0.97), $p < 0.001$). Unlike in the combined sample, tDCS condition was significant (*b*(SE) = -94.22(39.99), $p = 0.022$), indicating that active stimulation decreased reaction times over and above the effect of accuracy. The main effect of performing the baseline/test in the MRI was also significant (*b*(SE) = -150.5(43.99), $p = 0.001$) (Table 6), while the interaction between block and tDCS condition was not significant (*b*(SE) = -20.84(10.47), $p = 0.052$). However, the model including the interaction effect had significantly better fit ($\chi^2(1) = 4.01$, $p = 0.045$) (Figure 9; Table 7). In the MCI group neither the main effect of tDCS condition (*b*(SE) = 44.54(67.15), $p = 0.523$), or the interaction between condition and block (*b*(SE) = 15.73(15.61), $p = 0.325$) were significant influences on reaction time. And unlike the combined and HC samples, the

main effect of performing the baseline/test blocks in the MRI (*b*(SE) = -67.28(71.74), *p* = 0.356), and the main effect of accuracy (*b*(SE) = -3.68(1.91), *p* = 0.054) were not significant.

Discussion

In the first application of active tDCS to the right IFG in older adults (Indahlastari, Hardcastle, et al., 2021a; Siegert et al., 2021), the current study observed an improvement in performance during a difficult discovery learning task. From baseline to test, those in the combined sample who received active stimulation improved an average of 11.3%, compared to an average of 4.0% in those who received sham stimulation. For HC alone, improvement with active stimulation was 12.3% compared to 5.1% in sham. MCI patients who received active stimulation had an 8.4% increase in performance from baseline to test, 7 times greater than those who received sham stimulation who had an average improvement of 1.2%.

It is notable that improvement was seen in older adults using a stimulation protocol previously successful in younger adults. Only a handful of studies have been conducted comparing the same tDCS protocols between younger and older adults, but differing effects of anodal stimulation between these populations is common (Habich et al., 2020). For example, during anodal stimulation applied during a resting state MRI scan, opposing patterns of functional connectivity changes were observed between younger and older adults, indicating that different physiological effects can follow from the same stimulation protocol (Antonenko, Nierhaus, et al., 2018). In another study, older and younger adults looked at pictures of famous places and people and were asked to recall the name. Anodal tDCS was applied to the left and right anterior temporal lobe (ATL) in a cross-over design. In face

recall an interaction occurred where older adults had greater improvement during left ATL stimulation, whereas younger adults had greater improvement during right ATL stimulation. When identifying places, older adults improved with both right and left ATL stimulation, while younger adult performance declined with both right and left ATL stimulation. These findings indicate that behavioral results can also differ across age groups receiving the same stimulation protocol (Ross et al., 2011). Together, different physical and behavioral consequences of stimulation in older adults fits with theoretical accounts of aging derived from fMRI, where older adults display more overall frontal lobe activation and more bi-hemispheric activation compared to younger adults (Davis et al., 2012; Hakun et al., 2015a; Turner & Spreng, 2012a)

Given the importance of age in tDCS application, a post-hoc analysis was performed with the current sample, regressing age on PRETXT test performance. Age was a significant predictor of performance on the test blocks in the active group, (R^2 = 0.098, β = -0.31, t(40) = -2.08, p = 0.044). There was no such relationship in the sham group (Figure 10). So, while the average age of those who received active anodal stimulation was 67.6 years, of those who had over 60% accuracy in the test blocks, 11 had ages lower than the average, while only 4 had ages above the average. By overall categorization accuracy, those lower in age appear to be the primary benefactors of active tDCS in the current study.

Nevertheless, a significant interaction between active tDCS and block was observed in the on-average older MCI group, where improvement in categorization occurred gradually over the training blocks, such that only in the last training block did the average performance of

active MCI subjects meaningfully separate from their sham counterparts. This compared to the HC group, where improvement was instant, with a gap in performance between active and sham stimulation occurring in the first training block. This difference could be due to tDCS of the rIFG improving different cognitive processes in younger and older subjects within our sample. In the younger HC sample, rIFG stimulation may be improving insight and creativity, processes that are associated with the rIFG stimulation area (Bowden & Jung-Beeman, 2003; Mashal et al., 2007; Mihov et al., 2010). As the rules that must be discerned in order to correctly categorize the pictures are arbitrary, having to do with how the picture is taken rather than anything in the picture itself, insight and creativity are key to success in the task. In addition to imaging studies, there is some evidence linking the rIFG with creativity via tDCS, from a study where both anodal and cathodal stimulation were each applied to the contralateral inferior frontal gyri concurrently, with rIFG anodal coupled with left IFG cathodal increasing creativity (Hertenstein et al., 2019; Mayseless & Shamay-Tsoory, 2015).

In the older MCI sample, delayed improvement could have occurred due to improvements in sustained attention, another process associated with the rIFG (Bowden & Jung-Beeman, 2003; Hampshire et al., 2009, 2010). Another way of conceptualizing attention over an extended period is as the vigilance decrement, which is a decrease in the ability to notice details over time (Helton & Russell, 2011; Parasuraman, 1979) that begins to occur around 20 minutes (Hitchcock et al., 2003). With the training portion of the PRETXT task occurring over 40 minutes, an increased ability to attend to details in the second half of the training could have provided a performance boost to those with MCI.

Stimulation also influenced reaction time, though this was only significant in the HC group. Notably, those in the HC group who received active anodal stimulation had faster reaction times when accuracy was controlled for, indicating that stimulation itself decreased reaction times. Of note, while the effect of accuracy decreased reaction times in both HC and those with MCI, the effect of active stimulation was reversed, where active stimulation decreased reaction times in the HC group by 94 milliseconds, but increased reaction times (though non-significantly) in the MCI group by 45 milliseconds. This difference in reaction times is further evidence for possible contrasting mechanisms in MCI and healthy control subjects in our sample.

It is possible that in another context, this difference engendered by active anodal tDCS could provide a meaningful benefit to those living with MCI. Harnessing the small effect of tDCS seen in the current study in those with MCI may require multiple applications of online tDCS, which is underexplored in the literature (Chen et al., 2022). Those studies that have used multiple applications of online tDCS in those with MCI have suffered from poor design, where online tDCS has been applied while subjects perform multiple tasks (Gonzalez et al., 2021; Martin et al., 2019). As a subthreshold neuromodulator, online tDCS can be said to be partially targeted towards neurons that are close to firing, i.e. engaged in that online task (Kronberg et al., 2017, 2019). As it may take up to 5 minutes for tDCS to affect neuronal excitability, changing the target of the tDCS current by changing the task multiple times during stimulation is likely to minimize any effect of tDCS (Bindman et al., 1964). Future tDCS application in those with MCI should thus explore online stimulation during a singular task, as in the current study. While this may hinder the transferability of any trained task, it

will provide additional evidence for the efficacy of tDCS in adults with MCI. With this established, tasks with the most utility for improving day-to-day function can then be explored.

Limitations

While the results provide tentative support for the efficacy of tDCS application in older adults, the magnitude of tDCS effect in this study is a smaller than that seen previously in the PRETXT task. Besides the differences in populations, there were modifications in the PRETXT task that could also account for differences in performance. While in the current version of the task there was one rule concerning traffic direction that subjects needed to learn in order to correctly categorize the pictures, in the previous version there was an additional rule present in half of the pictures, where an *umlaut* was associated with left sided traffic and a *tilde* with right sided traffic. It is unclear what effect the removal of this rule could have had, and it is possible that the absence of it made the task either easier or more difficult.

It is noteworthy that subjects who completed the baseline and test blocks in the fMRI had different accuracy and reaction times than those who completed these blocks outside the scanner, a possibility that was not anticipated when designing the study. Examining test data only, across HC and MCI groups those who completed these blocks in the scanner had an average accuracy of 57.9% (SD=17.3%; n=29, 31% MCI) compared to those who completed these outside the scanner who had an average accuracy of 63.6% (SD=18.2%; n=14, 29% MCI). Curiously, this pattern was reversed for those who received sham stimulation, with

those in the scanner performing better at 55.2% (SD=12.9%; n=26, 27% MCI) than those performing the test outside at 50.6% (SD=12.4%; n=9, 44% MCI). This pattern is likely attributable to the small sample size in the latter group, which was also comprised of a larger percentage of those with MCI, rather than any interaction with stimulation. Being in the scanner had a more uniform impact on reaction times between stimulation groups. While the effect of being in the MRI was negligible during the test blocks, reaction times at baseline were significantly different inside and outside the scanner. Within the scanner the average response time in milliseconds at baseline was 921.9 (SE=43.1; n=58. 29% MCI), compared to outside the scanner where it was 1295.2 (SE=48.9; n=24, 33% MCI). While the instructions given to participants outside and inside the scanner were identical, several other differences may account for the discrepancies seen in reaction time as well as accuracy inside and outside the scanner.

One difference was the experimental design. Those completing the task outside the scanner performed all 9 blocks consecutively within the span of 2 hours. For those who received an MRI, the baseline portion of the PRETXT task was performed on a separate day from the other blocks. Most often these different experimental visits were within the same week, but in a few instances several months separated the visits. It is possible that receiving active tDCS immediately after the baseline portion garnered some benefit as those who received active tDCS and were tested outside the scanner had an increase in categorization accuracy from baseline at 48.4% (SE=2.1%) to training block 1 at 55.7% (SE=3.4%), while active/inside MRI (baseline: 50%, SE=1.4%; training 1: 48.2%, SE=2.7%), sham/outside MRI (baseline: 47.1%, SE=1.7%; training 1: 44.2%, SE=2.9%), and sham/inside MRI

(baseline:52.4%, SE=1.2%; training 1: 47.7%, SE=1.5%) all had declines from baseline to training 1 (Figure 11). The reason for these differences is unclear, and *a priori* it could have been hypothesized that a gap in time between baseline and training block 1 could have benefited performance through an incubation period, where the solution to an unsolved problem emerges suddenly after having set aside thinking about that problem for a time (Wallas, 1926). However, besides the results themselves, several other factors argue against a possible benefit for an incubation period. First, there may be an ideal ratio of time spent in purposeful problem solving and the incubation period (Sio & Ormerod, 2009). For an incubation period where activity is totally unrelated to problem solving, the typical ratio is 10:1, that is, 1 unit of active problem solving to 10 units of an incubation period (Kaplan, n.d.). In the current study that ratio was at the very least 144:1 (with 10 minutes of active problem solving and an incubation period of 24 hours), likely too disproportionate to engender insight through incubation. Second, failure in problem solving might be crucial, where only those problems where an impasse is reached are remembered sufficiently to engender problem solving during incubation (Patalano & Seifert, 1994; Zeigarnik, 1938). As participants in the baseline portion had not yet received accuracy feedback, they had no way of gauging their ability to correctly categorize the pictures, and no way of knowing if they had reached an impasse.

For those who received active stimulation and were tested inside the scanner, there was also a larger decrease in performance between training block 4 and the test blocks, an average decrease of 3.56% compared to 0.88% in active/outside MRI, 0.28% in sham/outside MRI, and 0.98% in sham/inside MRI (Figure). As with the time between baseline and the first

training session, there was a gap between training block 4 and test block 1 for those receiving an MRI, albeit a much shorter gap ranging from around 15 minutes to around 60 minutes. While it is unknown what specific cognitive processes might benefit from tDCS-mediated improvement and allow for increased categorization accuracy on the PRETXT task, it is possible that tDCS mediated effects after online application outlast the duration of stimulation and provide beneficial after effects. For example, if tDCS elicited improvements in processes such as sustained attention or increased processing speed, these effects could persist during the test blocks and continue to provide benefit. In the motor cortex, increases in cortical excitability following stimulation have been shown to endure for 30-60 minutes (Ammann et al., 2017; López-Alonso, Cheeran, et al., 2015; López-Alonso, Fernández-del-Olmo, et al., 2015). Though these results are highly variable, and it is unclear to what extent this variability is due to the effect of tDCS itself or in the common method of measuring motor cortex excitability, TMS motor evoked potentials (Chew et al., 2015), it is likely that the physiological effects of tDCS in the current study lasted beyond the period of stimulation itself. Those who had to wait and perform the test portion in the scanner then experienced a diminished extended benefit of tDCS compared to those who performed the test blocks immediately after the end of stimulation.

The last major difference that likely accounted for variability in performance between those inside and outside the scanner was the size and quality of the display on which subjects viewed the stimuli. Inside the scanner, the projected image, while smaller, actually took up a greater proportion of the visual field. However, rather than make it easier, this might have made it more difficult for participants to discern the street direction rule, which rather than

requiring visual search requires subjects to view the entire picture as a whole. Within the scanner the screen is also partially transparent as it is a projected rather than digital display, leading to a distorted image in which details are more difficult to discern. This, in combination with a distracting setting and an older population, likely made a difference in performance. Older adults have difficulty seeing as well as younger adults when there is reduced light due to a phenomenon called senile miosis where the pupil becomes smaller and allows less light to enter the eye (Stuen & Faye, 2003). In the low-light setting of the MRI scanner, this may have made it difficult for older adults to discern the stimuli (Sloane et al., 1988). Additionally, it is well documented that processing speed declines in older adults (Harada et al., 2013), and there is evidence to indicate that the presence of distractions further hinders processing speed in older adults (Lustig et al., 2006; Weeks & Hasher, 2014). The distracting environment of the MRI may have then put a further burden on the performance of older adults.

Future Directions

The relationship between age and performance seen in the current study is undoubtedly driven by changes in anatomy and physiology, as the brain changes in a predictable way as it ages and these changes affect the efficacy of tDCS. Across age groups, the effects of tDCS are highly variable and affected by numerous experimental and individual factors (Batsikadze G. et al., 2013; Nitsche et al., 2003), but due to changes in brain morphology, variability is an even greater concern when applying tDCS in older adults (Siegert et al., 2021). Critically, the thickness of the cortex decreases with age (Hogstrom et al., 2013; Salat et al., 2004a), with the PFC, the tDCS target in the current study, the first to undergo age

associated atrophy (Nissim et al., 2017a). This poses a problem for tDCS, as the increasing gap between the skull and the cortex is filled by highly conductive cerebrospinal fluid (CSF). In this case more of the current introduced by tDCS travels around the brain via the CSF rather than into the cortex below the electrode (Indahlastari, Hardcastle, et al., 2021a; Mahdavi & Towhidkhah, 2018a). The age effects observed in the current study could largely be due to cortical atrophy and the accompanying increase in CSF. Understanding how these anatomical changes influence this protocol in older adults is vital to maximizing the benefits observed with the F10 protocol.

Conclusion

In the first application of the F10 protocol in older adults, tDCS was successful in improving performance on a difficult categorization task. The effects of this protocol were different across younger and older members of our sample, with the on-average younger HC sample seeing an immediate benefit to performance following tDCS application, and the on-average older MCI sample seeing a benefit following 20 minutes of application. Age was also predicative of performance across groups, but only in the active stimulation group, indicating that the benefits of tDCS are dependent upon changes that occur with aging. Future work should seek to elucidate the anatomical and physiological differences that mediate the relationship between age and tDCS outcome.

Figures

Figure 1: Project design for PRETXT participation for subjects who received an MRI.

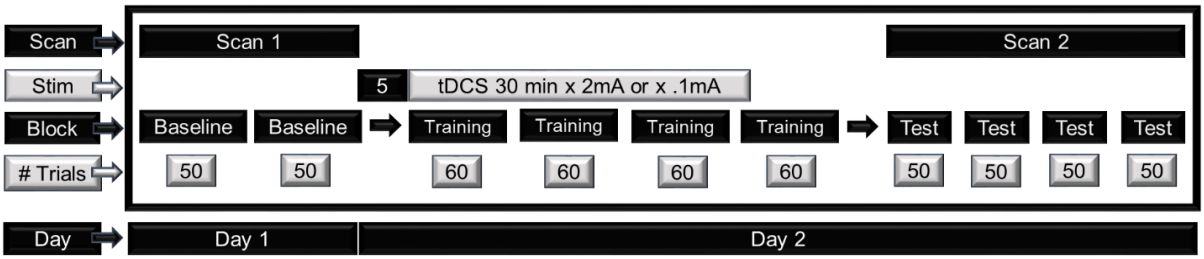


Figure 2: Project design for PRETXT participation for subjects who did not receive and MRI.

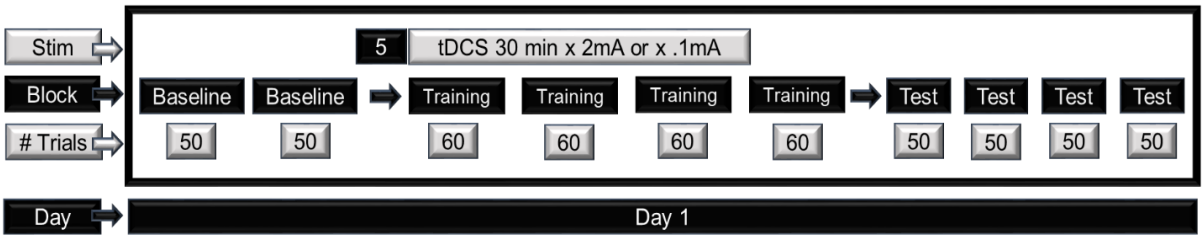


Figure 3: Sensation ratings for active and sham groups 30 seconds and 5 minutes after the start of stimulation. Error bars +/- 1 SE

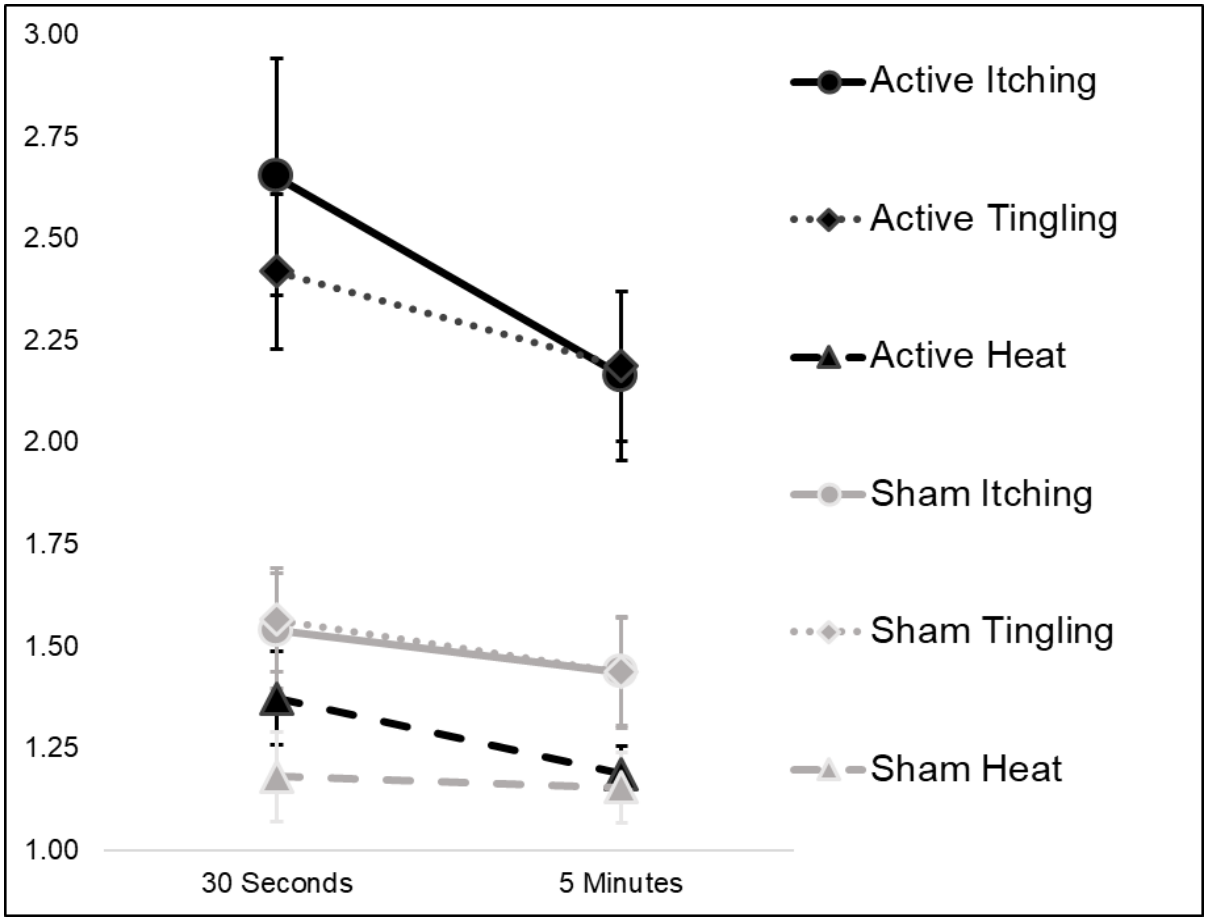


Figure 4: Accuracy for the combined sample across active and sham groups. Error bars +/- 1 SE.

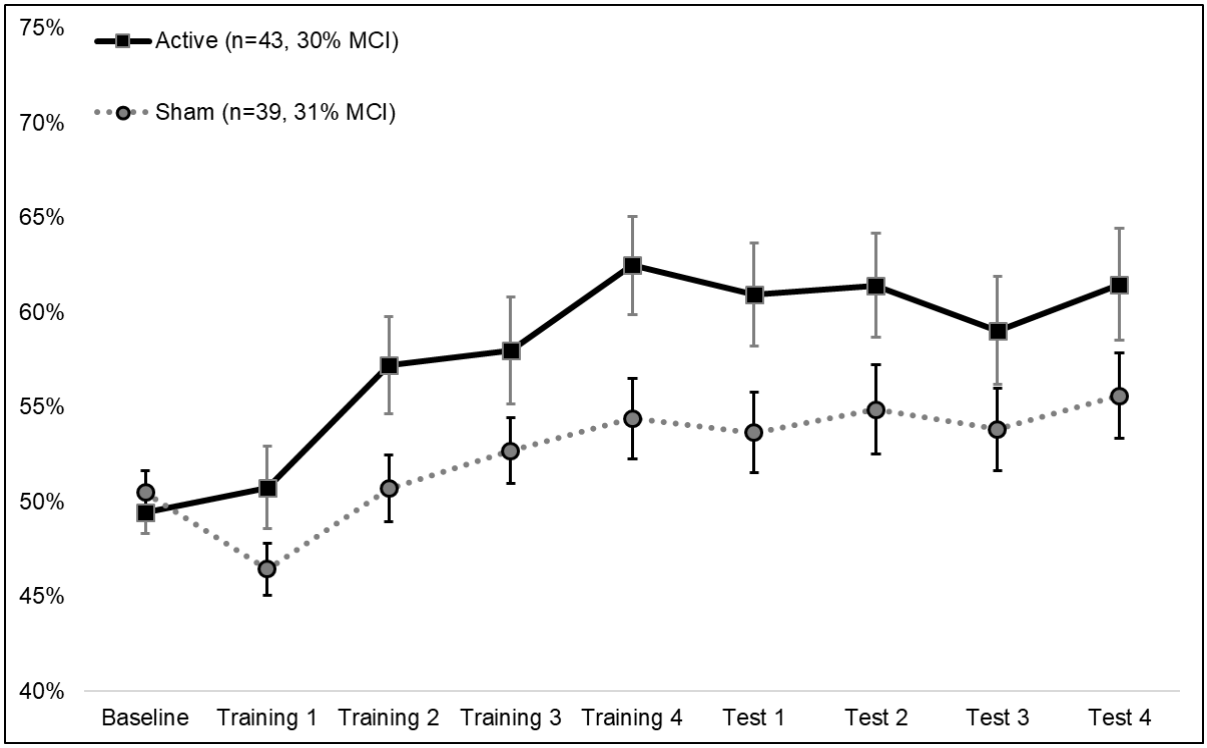


Figure 5: Accuracy for the healthy control group across active and sham groups. Error bars +/- 1 SE.

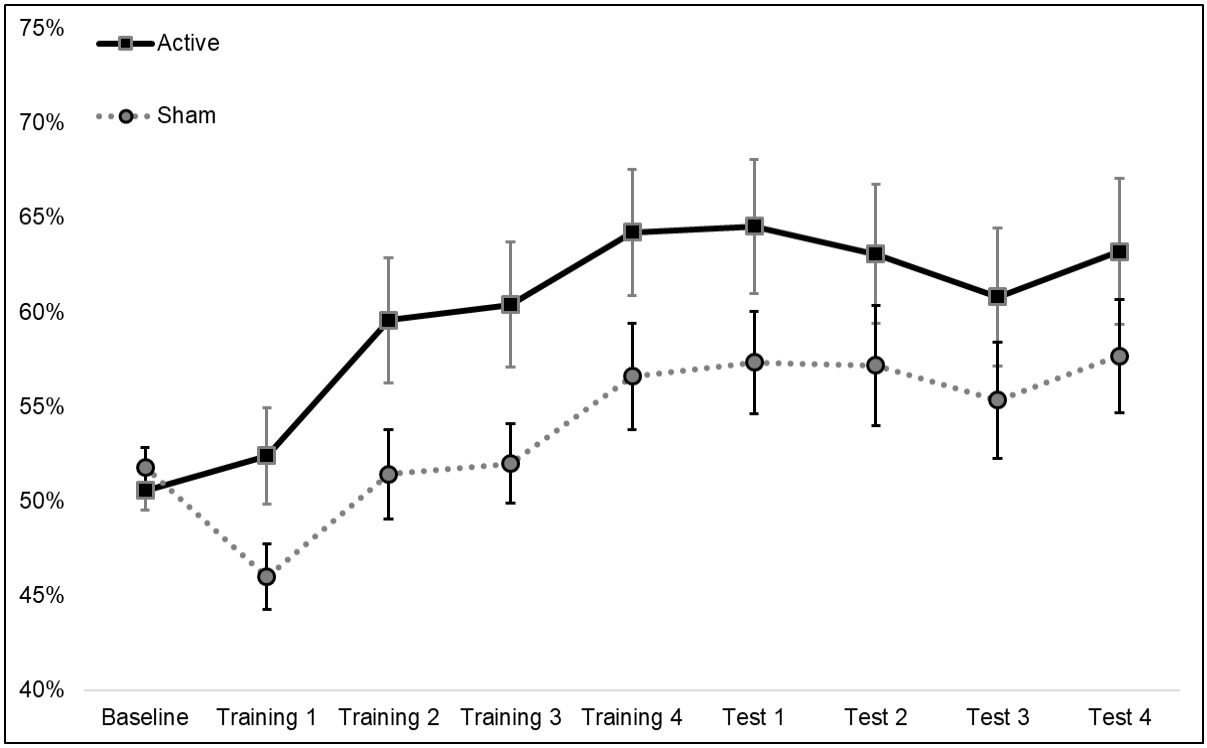


Figure 6: Accuracy for the MCI group across active and sham groups. Error bars +/- 1 SE.

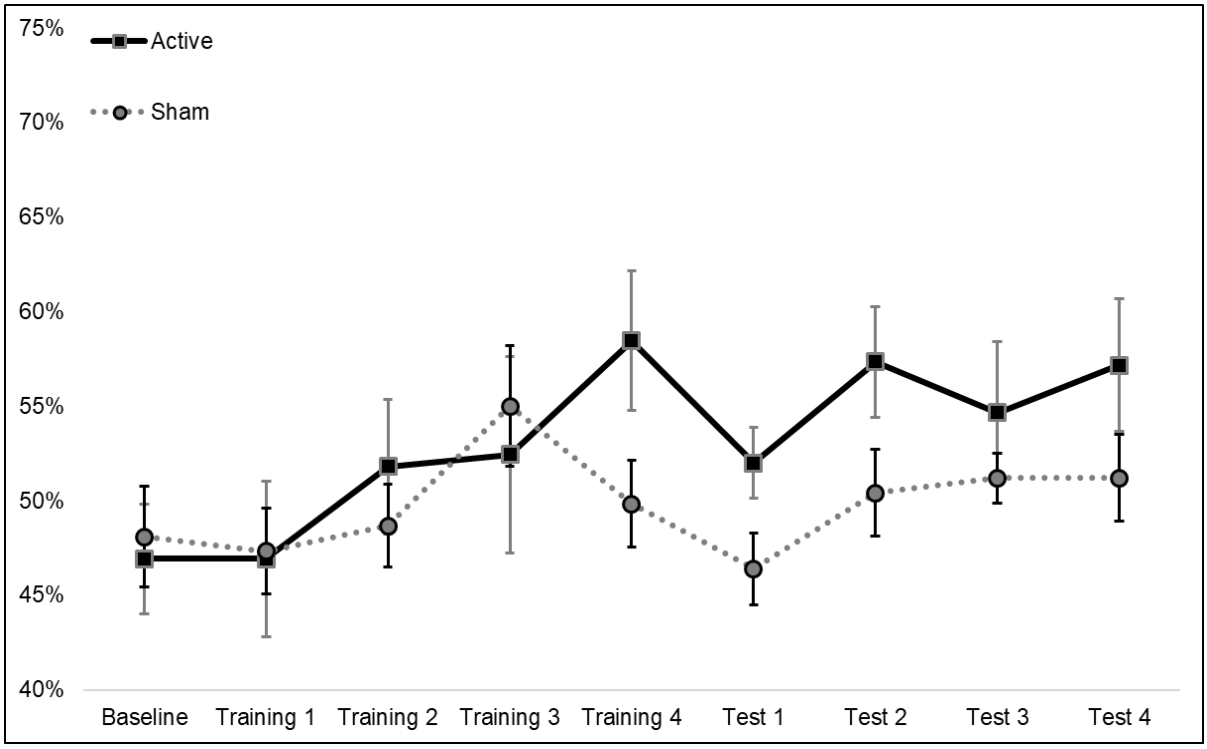


Figure 7: Reaction time for the combined groups across active and sham groups. Error bars +/- 1 SE.

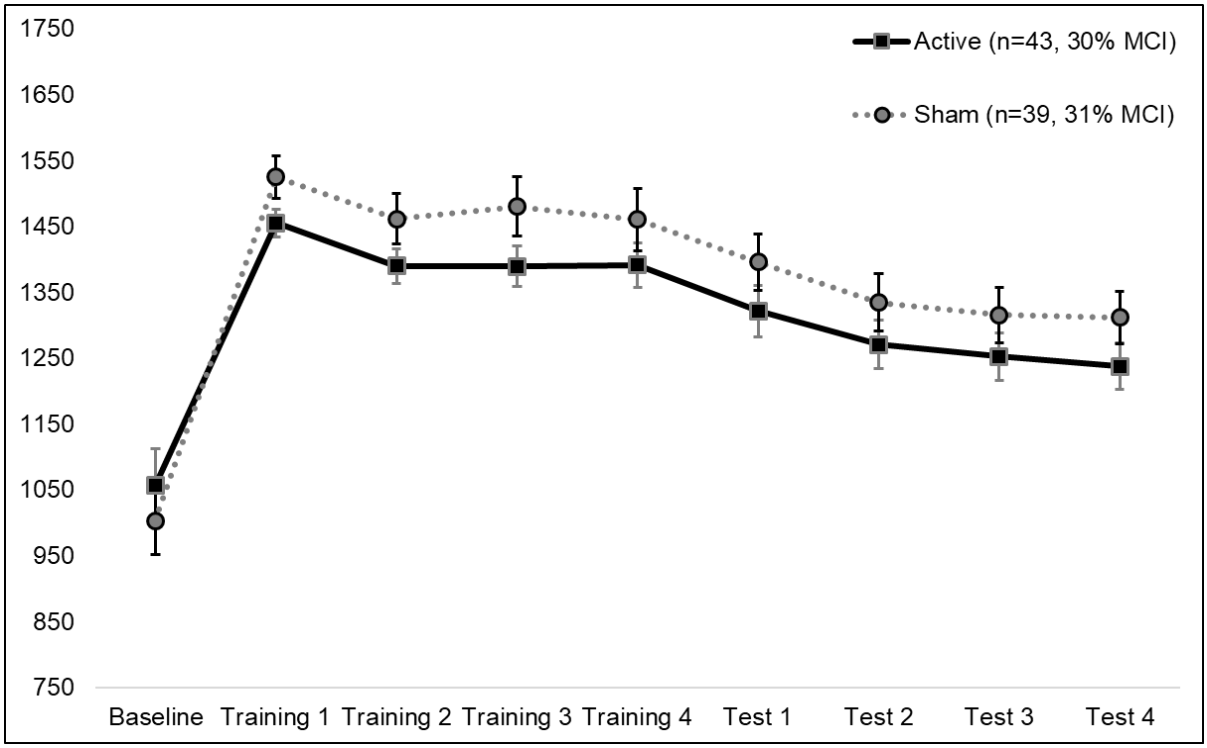


Figure 8: Reaction time for the healthy control group across active and sham groups. Error bars +/- 1 SE.

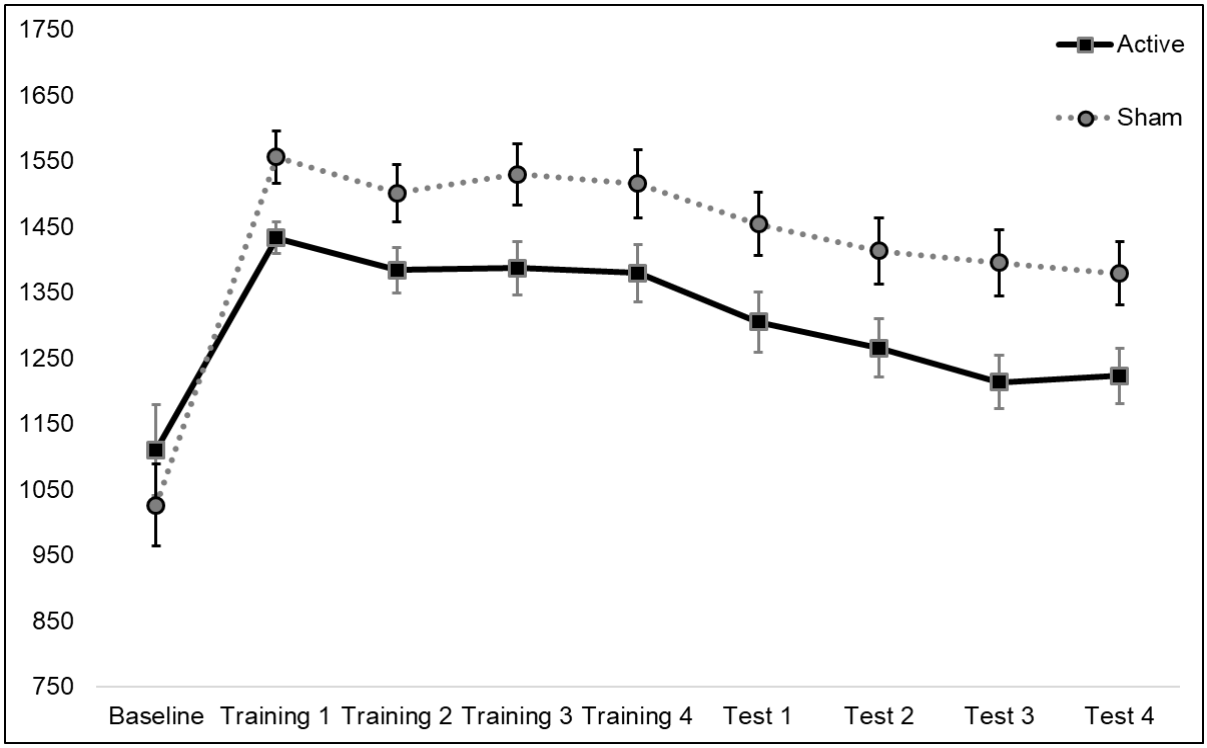


Figure 9: Reaction time for the MCI across active and sham groups. Error bars +/- 1 SE.

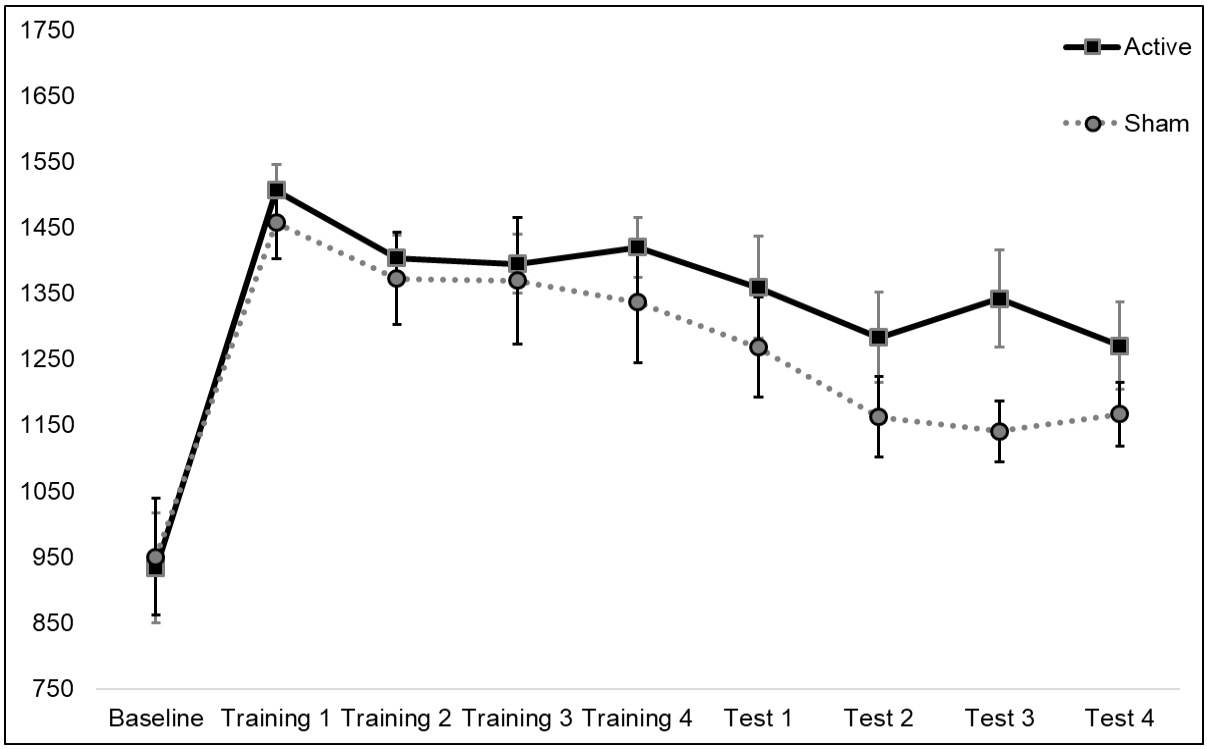


Figure 10: The relationship between age and average PRETXT test performance.

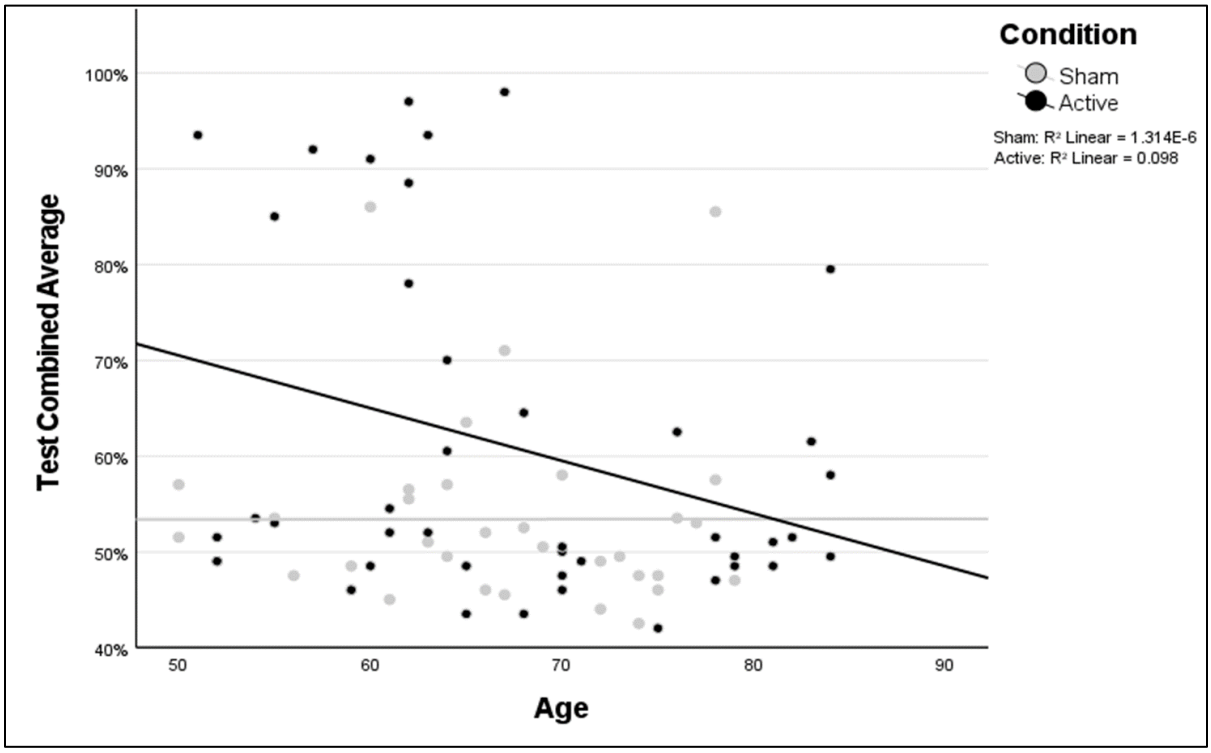
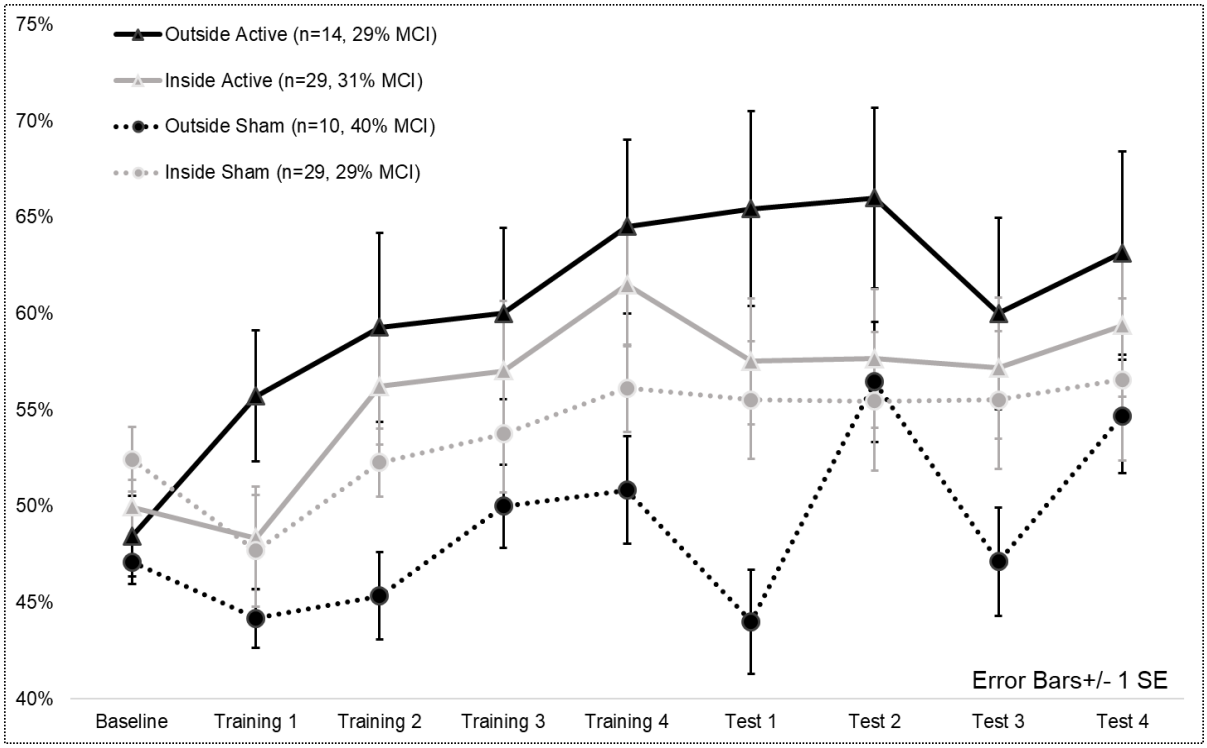


Figure 11: Differences in accuracy by tDCS condition and whether baseline/test were performed within the fMRI. Error bars = +/- 1 SE.



Tables

Table 1: *Sample Demographics*

	Total (N=82)	Healthy Control (n=57)	Mild Cognitive Impairment (n=25)
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)
Age	66.9 (9.1)	63.9 (7.3)	73.8 (8.9)
Female Sex	45 (55%)	38 (66%)	7 (28%)
Male	37 (45%)	19 (33%)	18 (72%)
Black	2 (2.4%)	1 (1.8%)	1 (4%)
Hispanic	17 (20.7%)	12 (21.1%)	5 (20%)
Native American	2 (2.4%)	2 (3.5%)	
White	61 (74.4%)	42 (73.7%)	19 (76%)

Table 2: *Results from the linear mixed model examining accuracy, HC and MCI combined*

	Main Effects				Interaction			
Fixed Effects	b (SE)	df	t-value	p-value	b (SE)	df	t-value	p-value
Intercept	**53.59 (1.64)**	**108.61**	**33.01**	**<0.001**	**52.13 (1.93)**	**85.66**	**27.07**	**<0.001**
Block	**1.14 (0.22)**	**79.19**	**5.15**	**<0.001**	**0.81 (0.32)**	**80.41**	**2.5**	**0.014**
Condition	3.07 (1.68)	80.17	1.83	0.072	**5.83 (2.58)**	**80.41**	**2.57**	**0.027**
MRI	0.43 (1.84)	79.83	0.231	0.818	0.42 (1.84)	79.85	0.23	0.819
Block x Condition					0.62 (0.44)	78.7	1.41	0.164

Random Effects	Variance	SD	Correlation with intercept	Variance	SD	Correlation with intercept
Intercept	129.3	11.37		128.58	11.34	
Block	2.87	1.69	0.92	2.84	1.69	0.92

Note: Bold font indicates associations that are significant ($p \leq .05$). b = unstandardized regression coefficient; SE = standard error; df = degrees of freedom; SD = standard deviation

Table 3: *Results from the linear mixed model examining accuracy in HC*

	Main Effects				Interaction			
Fixed Effects	b (SE)	df	t-value	p-value	b (SE)	df	t-value	p-value
Intercept	**54.24 (2.06)**	**78.14**	**26.33**	**<0.001**	**53.47 (2.55)**	**59.7**	**20.96**	**<0.001**
Block	**1.36 (0.28)**	**56**	**4.71**	**<0.001**	**1.96 (0.43)**	**56.73**	**2.8**	**0.007**
Condition	**4.78 (1.94)**	**55.05**	**2.46**	**0.017**	**6.24 (3.42)**	**55.54**	**1.83**	**0.073**
MRI	0.38 (2.16)	55.01	0.18	0.859	0.38 (2.16)	55.02	0.18	0.862
Block x Condition					0.3 (0.58)	55.26	0.52	0.607

Random Effects	Variance	SD	Correlation with intercept	Variance	SD	Correlation with intercept
Intercept	156.18	12.5		157.68	12.56	
Block	3.56	1.89	0.96	3.62	1.9	0.96

Note: Bold font indicates associations that are significant ($p \leq .05$). b = unstandardized regression coefficient; SE = standard error; df = degrees of freedom; SD = standard deviation

Table 4: *Results from the linear mixed model examining accuracy in MCI*

	Main Effects				Interaction			
Fixed Effects	b (SE)	df	t-value	p-value	b (SE)	df	t-value	p-value
Intercept	**50.36 (2.18)**	**22.52**	**23.12**	**<0.001**	**49.41 (2.23)**	**21.78**	**22.13**	**<0.001**
Block	**0.64 (0.27)**	**21.97**	**2.32**	**0.029**	0.02 (0.37)	21.25	0.06	0.951
Condition	2.59 (2.88)	21.98	0.9	0.377	4.39 (3.02)	21.67	1.46	0.159
MRI	-0.12 (3.08)	21.92	-0.04	0.969	-0.07 (3.09)	21.94	-0.02	0.983
Block x Condition					**1.17 (0.51)**	**21.22**	**2.3**	**0.032**

Random Effects	Variance	SD	Correlation with intercept	Variance	SD	Correlation with intercept
Intercept	48.86	6.99		49.53	7.04	
Block	0.78	0.88	0.42	0.55	0.74	0.48

Note: Bold font indicates associations that are significant ($p \leq .05$). b = unstandardized regression coefficient; SE = standard error; df = degrees of freedom; SD = standard deviation

Table 5: *Results from the linear mixed model examining response time, HC and MCI combined*

	Main Effects				Interaction			
Fixed Effects	b (SE)	df	t-value	p-value	b (SE)	df	t-value	p-value
Intercept	**1381.43 (28.68)**	**83.72**	**48.17**	**<0.001**	**1389.14 (29.57)**	**81.07**	**46.98**	**<0.001**
Block	5.29 (4.45)	82.06	1.19	0.237	10.31 (6.42)	77.54	1.61	0.112
Condition	-40.51 (36.4)	79.18	-1.11	0.269	-54.57 (38.67)	79.51	-1.41	0.162
Accuracy	**-3.72 (0.88)**	**497.84**	**-4.21**	**<0.001**	**-3.66 (0.89)**	**496.94**	**-4.14**	**<0.001**
MRI	**-117.17 (39.67)**	**77.54**	**-2.95**	**0.004**	**-117.24 (39.69)**	**77.34**	**-2.95**	**0.004**
Block x Condition					-9.41 (8.71)	74.75	-1.08	0.283

Random Effects	Variance	SD	Correlation with intercept	Variance	SD	Correlation with intercept
Intercept	24563.7	156.73		24620.7	156.91	
Block	738.4	27.17	0.49	744.2	27.28	0.49

Note: Bold font indicates associations that are significant ($p \leq .05$). b = unstandardized regression coefficient; SE = standard error; df = degrees of freedom; SD = standard deviation

Table 6: *Results from the linear mixed model examining response time in HC*

	Main Effects				Interaction			
Fixed Effects	b (SE)	df	t-value	p-value	b (SE)	df	t-value	p-value
Intercept	**1439.67 (31.71)**	**54.12**	**45.4**	**<0.001**	**1439.67 (31.71)**	**54.12**	**45.4**	**<0.001**
Block	6.96 (5.47)	56.57	1.27	0.208	6.96 (5.47)	56.57	1.27	0.208
Condition	**-94.22 (40)**	**52.37**	**-2.36**	**0.022**	**-94.22 (40)**	**52.37**	**-2.36**	**0.022**
Accuracy	**-4.12 (0.97)**	**248.98**	**-4.27**	**<0.001**	**-4.08 (0.96)**	**249.99**	**-4.24**	**<0.001**
MRI	**-150.49 (43.99)**	**248.97**	**-3.42**	**0.001**	**-150.67 (43.93)**	**50.88**	**-3.43**	**0.001**
Block x Condition					**-20.84 (10.47)**	**51**	**-1.99**	**0.052**

Random Effects	Variance	SD	Correlation with intercept	Variance	SD	Correlation with intercept
Intercept	18348.3	135.46		18231.5	135.02	
Block	850.6	29.17	0.35	798.1	28.25	0.35

Note: Bold font indicates associations that are significant ($p \leq .05$). b = unstandardized regression coefficient; SE = standard error; df = degrees of freedom; SD = standard deviation

Table 7: *Results from the linear mixed model examining response time in MCI*

	Main Effects				Interaction			
Fixed Effects	b (SE)	df	t-value	p-value	b (SE)	df	t-value	p-value
Intercept	**1278.71 (51.82)**	**23.64**	**23.54**	**<0.001**	**1262.98 (53.87)**	**21.43**	**23.44**	**<0.001**
Block	3.33 (7.79)	22.86	0.43	0.673	-4.69 (11.15)	21.09	-0.42	0.678
Condition	44.54 (67.15)	21.96	0.65	0.523	73.57 (73.15)	21.45	1.01	0.326
Accuracy	-3.68 (1.91)	207.25	-1.93	0.054	**-3.96 (1.93)**	**205.44**	**-2.05**	**0.041**
MRI	-67.28 (71.74)	21.82	-0.94	0.356	-67.16 (71.55)	21.83	-0.94	0.358
Block x Condition					15.73 (15.61)	21.73	1.01	0.325

Random Effects	Variance	SD	Correlation with intercept	Variance	SD	Correlation with intercept
Intercept	27269.6	165.14		27003.6	164.33	
Block	584.9	24.19	0.64	592.5	24.34	0.63

Note: Bold font indicates associations that are significant ($p \leq .05$). b = unstandardized regression coefficient; SE = standard error; df = degrees of freedom; SD = standard deviation

Appendix

Accuracy formula for linear mixed model using lmer in R:

Summary(Main Effects <- lmer(Accuracy ~ Block (Centered) + Condition + fMRI Group + (Block Centered|Subject ID), control=lmerControl(optimizer="bobyqa",optCtrl=list(maxfun=2e5)),data=LONG,na.action=na.omit))

Summary(Interaction Effects <- lmer(Accuracy ~ Block (Centered)*Condition + fMRI Group + (Block Centered|Subject ID), control=lmerControl(optimizer="bobyqa",optCtrl=list(maxfun=2e5)),data=LONG,na.action=na.omit))

ANOVA(Main Effects, Interaction Effects)

Response time formula linear mixed model using lmer in R:

Summary(Main Effects <- lmer(Response Time ~ Block (Centered) + Condition + Accuracy + fMRI Group + (Block Centered|Subject ID), control=lmerControl(optimizer="bobyqa",optCtrl=list(maxfun=2e5)),data=LONG,na.action=na.omit))

Summary(Interaction Effects <- lmer(Response Time ~ Block (Centered)*Condition + Accuracy + fMRI Group + (Block Centered|Subject ID), control=lmerControl(optimizer="bobyqa",optCtrl=list(maxfun=2e5)),data=LONG,na.action=na.omit))

ANOVA(Main Effects, Interaction Effects)

Interaction between Anatomy and Transcranial Direct Current Stimulation (tDCS) on Category Learning in Older Adults

Abstract

Transcranial direct current stimulation is an emerging technology possibly capable of improving cognitive function in older adults, both those with and those without pathological conditions associated with aging. However, a major hindrance to tDCS application in older adults are brain changes that occur with aging, specifically the shrinking of the cortex, which makes it more difficult for the current introduced by tDCS to reach the brain. Finite element modeling (FEM) of current flow based on individual structural images provides a method of mapping current flow, allowing an understanding of the interaction between tDCS, anatomy, and performance. The current study performed FEM in a sample of older adults with and without Mild Cognitive Impairment and explored the relationship between current delivered to the right inferior frontal gyrus via anodal tDCS and performance on a difficult categorization task. Analyses were performed in order to understand differences between the MCI and healthy control group, differences in brain ratio, age, and performance among all subjects, and differences in brain ratio, electric field magnitude and performance among those who received active anodal tDCS. Significant differences in white matter (WM), grey matter (GM), and cerebrospinal fluid (CSF) differentiated those classified as HC and those classified as having MCI with the latter having higher CSF and lower WM and GM ratios. Age was a significant predictor of WM, GM, and CSF ratios, with increasing age predicting smaller WM and GM ratios and a larger CSF ratio. Among those in the active group, significant relationships existed between WM and CSF ratios and categorization task performance, with higher WM and lower CSF ratios predicting better performance in the

active but not sham groups. Lastly, higher electric field magnitude underneath the electrode was predictive of better categorization task performance in the active group. The current study adds to the FEM literature, demonstrating that brain ratio is also predictive of performance in those receiving tDCS, in addition to electric field magnitude. Future research should attempt to fill the gaps in the FEM literature, conducting more prospective FEM studies, and further accounting for the utility of anatomy in customizing current dose *a priori*.

Introduction

Normal aging is generally associated with a decline in cognitive functioning, especially in measures of fluid intelligence such as processing speed, attention, memory, and executive function (Salthouse, 2010, 2012). Additionally, up to a fifth of those over the age of 65 are diagnosed with Mild Cognitive Impairment (MCI), with around 10% of those with an MCI diagnosis later progressing to Alzheimer's Disease (Kirova et al., 2015). Unfortunately, the best way to address cognitive decline currently is prevention, and the choice of the more salubrious option throughout life, be it consuming fewer deleterious substances or participating in more activities thought to increase cognitive reserve (Livingston et al., 2020). Once cognitive decline becomes apparent, existing interventions to stave of cognitive decline are less effective (Shafqat, 2008). A technology that can potentially improve this situation is transcranial direct current stimulation (tDCS), which offers one method of potentially opposing both normal cognitive decline and that seen in pathological conditions associated with aging. Promising results following tDCS application in older adults have been observed, indicating that tDCS is capable of providing a meaningful benefit in the cognitive functioning of older adults (Hsu et al., 2015; Manenti et al., 2013; Meinzer et al., 2013; Nissim, O'Shea, Indahlastari, Kraft, et al., 2019).

However, changes associated with the aging brain make the application of tDCS more difficult in older adults. With changes in imaging measures across both task-specific activation patterns (Davis et al., 2012; Goh, 2011; Hakun et al., 2015b) and resting state patterns (Betzel et al., 2014), as well as changes in neuronal function (Kumar & Foster, 2004; Randall et al., 2012; Tanabe et al., 1998), tDCS protocols that have been shown to be

effective in younger populations may not replicate in older samples, meaning that protocols must be specifically tailored. Aging is generally associated with structural and functional changes to the brain, with brain atrophy perhaps the most salient change (Drag & Bieliauskas, 2010). The thickness of the cortex decreases with age (Hogstrom et al., 2013; Salat et al., 2004b), with the prefrontal cortex (PFC) the first to see age associated atrophy, with decline there occurring faster than in other cortices (Nissim et al., 2017b). These brain volume changes are driven by decreases in both grey matter (GM) and white matter (WM) (Raz, 2005; Raz et al., 1997), decreases which accelerate with age (Oschwald et al., 2020). A measurable benchmark of brain atrophy is enlargement of the ventricles, which have a yearly median expansion rate of 0.43% for those aged 24 to 37 years, increasing to 4.25% yearly in those 70-81 (Betzel et al., 2014). Shrinking of the cortex also leads to increased space between the scalp and the brain, space which is then filled with greater amounts of cerebrospinal fluid (CSF). This poses a problem for tDCS application as CSF is highly conductive, leading to more of the current introduced by tDCS being shunted around the brain rather than into the brain (Mahdavi & Towhidkhah, 2018b). Atrophy varies across individuals, increasing the inter-individual variability of tDCS effects in older adults (Antonenko et al., 2021; Antonenko, Külzow, et al., 2018). As noted, the PFC is the first region to see atrophy, and it is the target for the vast majority of tDCS studies in older adults, furthering heterogeneity in outcomes (Indahlastari, Hardcastle, et al., 2021b; Lemaitre et al., 2012).

One way to try and understand the impact that different brain morphologies have on tDCS is to model the likely path of current through the skull via finite element modeling (FEM)

(Bikson et al., 2015; Datta et al., 2009). The first FEM models created to try and understand tDCS current flow were simple spheres, nested within one another to represent skin, skull, and brain (Miranda et al., 2006). Structural images, first combined into averaged, representative models and then taken from each individual, were then used as a basis, with these divided into different tissue types including grey matter (GM), white matter (WM), CSF, and bone, all assigned different conductivity values (Datta et al., 2009; Wagner et al., 2007). Added to these models was information about the physical properties of the electrodes and the tDCS dose. The end result are models containing many millions of elements (Bikson et al., 2012). The typical currents seen in these models mirror those seen in intracranial recordings (Opitz, Falchier, Yan, Yeagle, Linn, Megevand, Thielscher, Deborah A., et al., 2016), and in direct comparison, FEM models of tDCS current flow have been shown to correlate $r = .81 \pm .12$ with in vivo electrical recordings done in epilepsy patients (Huang et al., 2017). Electric fields predicted by FEM models have also been shown to correlate with physiological measures of tDCS effects, such as reductions in GABA concentration, a neurotransmitter involved in learning via long-term potentiation (Antonenko et al., 2019; Trepel & Racine, 2000), and stronger post-tDCS transcranial magnetic stimulation-induced motor-evoked potentials (Mosayebi-Samani et al., 2021), a common method of measuring the impact of tDCS since the reemergence of the technology in at the beginning of the century (Nitsche & Paulus, 2000).

Different FEM studies have attempted to quantify the degree to which tDCS current flow is affected by anatomical changes in aging. Several modeling studies with small sample sizes have demonstrated a trend of decreasing electrical field and current density in the brain with

increasing age (Mahdavi & Towhidkhah, 2018b; Thomas et al., 2018), and these findings have been corroborated by replications with larger samples. One study conducted with 24 adult males found that increasing age was significantly correlated with an increasing volume of CSF, and a decreasing amount of tDCS current reaching the cortex (Laakso et al., 2015). Notably, the range of ages used in this sample was 21-55 years old, meaning that brain changes may alter tDCS current flow in middle age as well as in older adults. Elsewhere, machine learning was able to predict responders and non-responders to tDCS among older adults using FEM modeling of current intensity, where current intensity was found to positively correlate with behavioral improvement in a working memory task (Albizu et al., 2020), a result that indicates that differences in the efficacy of tDCS across older participants might be reduced by the customization of applied current.

In the largest exploration of tDCS FEM in aging adults, Indahlastari and colleagues used structural images of 587 older adults, both males and females with an age range of 51-95, to model two tDCS electrode montages (Indahlastari et al., 2020). They computed brain ratio by taking the total volume inside the skull and dividing this by combinations of GM, WM, and CSF. They found that a negative correlation between age and current reaching the cortex underneath the electrode was due in part to an increasing quantity of CSF. The relationship between decreasing current flow and increasing CSF was not uniform across the brain, however, as there was a high degree of variability in atrophy across brain regions. The prefrontal cortex experienced the largest decreases in current density, a result that fits with the literature that sees this area as most prone to atrophy (Fjell et al., 2009; Nissim et al., 2017b). Given the prevalence of tDCS application to this area (Tremblay et al., 2014), it is

vital to account for atrophy when applying tDCS to samples of older adults, especially when trying to recreate montages previously successful in younger samples. Indahlastari et al. additionally found that reductions in grey matter drove the overall reduction in brain ratio seen with atrophy, while the relationship between white matter ratio and age was slightly positive. This latter finding is at odds with what has generally been observed elsewhere (Oschwald et al., 2020), but the large sample size lends credence to their findings. Additionally, if the decrease in GM outpaces that seen in WM, WM ratio could stay the same while the overall volume of WM declines.

One tDCS protocol previously successful in improving cognition in younger adults is active anodal application to the right inferior frontal gyrus (rIFG) coupled with cathodal application to the left arm (Clark et al., 2012; Coffman et al., 2012; Falcone et al., 2012). This protocol applied during a categorization task known as the PRETXT task (Gibson et al., 2020), has also recently been successful in improving performance in a sample of older adults between the ages of 50 and 84 (Study 1). The current study will build on those results by examining the relationship between brain ratio and age across a subset of participants who received structural magnetic resonance imaging (MRI), and on brain ratio, task performance, and electric field magnitude across those who received structural MRIs and active tDCS.

Methods

Healthy older adults, as well as those with MCI, were recruited for this study, and all data were collected at the Mind Research Network in Albuquerque, New Mexico. Inclusion

criteria required subjects to be: right handed; between 50-90 years old; an English speaker before the age of 7; without excessive drug or alcohol use, without a history of psychiatric hospitalization; without a history of epilepsy, migraines, stroke, traumatic brain injury, other chronic illnesses, or current COVID-19 symptoms; inexperienced with tDCS; and able to receive a MRI. Healthy control subjects were not allowed to be taking medications with significant psychotropic effects, but this requirement was waived for participants with MCI. MCI patients also needed to be able to sign a consent form, or have a legally authorized representative able to sign on their behalf. Both those who came with an existing diagnosis of MCI as well as those who scored a 26 or lower on the Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005b) were classified as having MCI for this study. All subjects were paid for their time at a rate of $10 dollars per hour and also received bonuses for completing each MRI ($25) and the entirety of the study ($10). Following consent, participation lasted 6-8 hours spread over two days (Figure 1). Subjects completed the first MRI scan on day 1, during which time they received the structural scan and performed the baseline portion of the PRETXT (Predicting Response To F10(X) tDCS) task. On day 2 they then received tDCS during the training portion of the PRETXT task followed by an additional MRI scan where the test portion of the PRETXT task was performed. The cognitive task (PRETXT) was a modified version of one used previously, in which subjects are tasked with learning how to categorize pictures of European streets into 2 categories. Learning occurs via feedback in the training portion, while the baseline and test portions performed in the scanner have no feedback. The cognitive task is explained in detail in study 1 and elsewhere (Gibson et al., 2020, 2021). Application of tDCS also followed the same pattern as that of previous studies, where an ActivaDose II iontophoresis unit was used to

apply 2 mA of anodal stimulation for 30 minutes to the rIFG, or F10 on the international 10/20 system, with the cathode placed on the contralateral triceps. The 5x5 cm sponges delivering the current were soaked in SignaGel for 24 hours prior to use, and the sponges were placed in a rubber holder with a metal backing during application. For double-blinding, two ActivaDose units were connected to a blinding box with 6 switches, half of which allowed the current from the ActivaDose machine administering the active dose of 2.0 mA to pass, while the other half allowed the current from the ActivaDose machine administering the sham dose of 0.1 mA to pass.

Finite Element Modeling of tDCS Current

T-1 and T-2 weighted images with 1 mm^3 volumes from 57 participants were used to create segmented brain models, and 29 of these (those who received active anodal stimulation) were subsequently used to create individual FEM models. T-2 weighted images were added, as comparison studies have demonstrated improved accuracy in models where T-2 images are included, especially in accurately demarcating CSF and bone (Hoornweder et al., 2022; Puonti et al., 2020). Realistic vOlumetric-Approach to Simulate Transcranial Electric Stimulation (ROAST) version 3.0 was used to create the FEM models (Huang et al., 2018). ROAST is a complete pipeline that runs in Matlab and borrows algorithms for tissue segmentation from SPM (Penny et al., 2011), the creation of a 3D mesh from Iso2mesh (Fang & Boas, 2009), and FEM solving from getDP (Dular et al., 1998). The assigned conductivity values used in ROAST to create the electric field distribution were (in Siemens per meter, S/m): Grey matter: 0.276; white matter: 0.126; CSF: 1.65; bone: 0.01; skin: 0.465; air: 2.5×10^{-14}; gel: 0.3; metal electrode backing for electrodes: 5.9×10^{7}. The tDCS

electrodes were modeled as 5 x 5 cm^2 pads with a thickness of 1 cm soaked in conductive gel. The anode was placed at F10, and the cathode was placed on the contralateral lower neck. This was accomplished by extending the field of view of the MRI with the ROAST program, and ascribing the conductivity value for skin to the modeled neck. While for montages involving only cephalic electrodes, imaging beyond the whole head makes only a negligible difference in computed electric field (Thomas et al., 2019), it is likely that small differences exist when modeling tDCS montages like that used in the current study where the return cathodal electrode is placed on the contralateral triceps. Segmented brain volumes were divided into WM, GM, and CSF, and these were used to calculate brain ratios, with either GM, WM, or CSF as the numerator and the combination of these three as the denominator.

Statistical Analysis and Hypotheses

Analyses were conducted in Statistical Product and Service Solutions (SPSS). Statistical analyses in the current study consisted of three one-way ANOVA's elucidating any differences in brain anatomy between those classified as MCI and those classified as HC, and then ten separate linear regression models exploring the relationship between age and brain ratio among all subjects scanned, brain ratio and electric field magnitude underneath the electrode in the active group, brain ratio and PRETXT performance in the active group, and finally between electric field magnitude underneath the electrode and PRETXT performance in the active group. Hypotheses for the models were the following:

1) Those classified as having MCI will have a significantly higher CSF ratio and significantly lower grey matter (GM) and white matter (WM) ratio compared to those classified as healthy controls.

2) A significant positive relationship will exist between CSF ratio and age.

3) A significant negative relationship will exist between GM ratio and age.

4) No significant relationship will exist between WM ratio and age.

5) In the active group, a significant negative relationship will exist between CSF ratio and electric field magnitude underneath the electrode.

6) In the active group, no significant relationship will exist between GM ratio and electric field magnitude underneath the electrode.

7) In the active group, a significant positive relationship will exist between WM ratio and electric field magnitude underneath the electrode.

8) In the active group, a significant negative relationship will exist between CSF and PRETXT test performance.

9) In the active group, no significant relationship will exist between GM ratio and PRETXT test performance.

10) In the active group, a significant positive relationship will exist between WM ratio and PRETXT test performance.

11) In the active group, a significant positive relationship will exist between electric field magnitude underneath the electrode (at Montreal Neurological Institute (MNI) coordinate 28, 23, -14) and PRETXT test performance.

Results

Subjects

Fifty eight subjects completed the protocol. Three of these were excluded, one active subject for pressing the wrong buttons during the test portion of the PRETXT task, one active subject for having electric field magnitudes 3 standard deviations above the mean, and one sham subject who was missing structural imaging. This left 55 subjects in total with an average age of 67.2 (SD = 8.9). A majority of the sample, n = 32 or 58.2%, were female and a majority of the sample n = 41 or 74.5%, identified as non-Hispanic white. There were 27 subjects included in the active anodal group, where again the majority were female, n = 15 or 55.6%, and identified as non-Hispanic white, n = 23 or (85.2%). Fifteen, or 27.3% of the entire sample were classified as having MCI, and n = 8 or 29.6% of the active group was classified as having MCI. See Table 1 for complete demographic information.

Differences according to study group and age

Three separate one-way ANOVAs were conducted to explore differences in brain ratios between those classified as having MCI and those classified as HC (Figure 2). MCI subjects (M = 33.2%, SD = 4.6%) in the current study had significantly higher CSF ratio ($F(1,53)$ = 18.39, $p < 0.001$) than HC subjects (M = 28.2%, SD = 3.6%). In contrast MCI subjects (M = 38.9%, SD = 2.4%) had a significantly lower GM ratio ($F(1,53)$ = 12.75, $p<.001$) than HC subjects (M = 41.3%, SD = 2.1%), and MCI subjects (M = 27.9%, SD = 3.1%) had a significantly lower ($F(1,53)$ = 12.45, $p<.001$) WM ratio compared to HC subjects (M =

30.5%, *SD* = 2.2%). For the regression models exploring the relationship between age and brain ratio, age explained more than half of the variance in CSF ratio (R^2 = 0.55), and the main effect of age on CSF was significant (β = -0.74, $t(53) = 8.07$, $p < 0.001$ (Table 2, Figure 3), with increasing CSF ratio with age. Age explained 44% of the variance in GM (R^2 = 0.44), and also had a significant main effect (β = -0.66, $t(53) = -6.45$, $p < 0.001$) (Table 2, Figure 4), where GM ratio increased with age. Similarly, age accounted for 39% of the variance in WM (R^2 = 0.39) and the main effect of age on WM ratio was significant (β = -0.62, $t(53) = -5.84$, $p < 0.001$) (Table 2, Figure 5), with WM ratio decreasing with age.

Differences in electric field magnitude and performance

In those who received active anodal stimulation, separate regression models indicated that CSF, GM, and WM all had significant main effects on electric field magnitude underneath the electrode. Within their respective models, CSF accounted for 39% of the variance (R^2 = 0.39), GM for 33% of the variance (R^2 = 0.33), and WM for 34% of the variance (R^2 = 0.34). The main effects were: CSF, (β = -0.63, $t(25) = -4.06$, $p < 0.001$) (Table 3, Figure 6); GM, (β = 0.57, $t(25) = 3.48$, $p = 0.002$) (Table 3, Figure 7); and WM, (β = 0.59, $t(25) = 3.62$, p = 0.001) (Table 3, Figure 8), where lower CSF and higher WM and GM ratios were associated with stronger electric fields underneath the electrode. For those in the active group, the main effects of CSF and WM ratio on PRETXT performance were significant, with CSF accounting for 21% of the variance (R^2 = 0.21, β =-0.46, $t(25) = -2.58$, $p = 0.016$) (Table 4, Figure 9) and WM 22% of the variance (R^2 = 0.22, β =0.47, $t(25) = 2.68$, $p = 0.013$) (Table 4, Figure 11) within their different models, such that lower CSF and higher WM ratios were associated with better performance. The main effect of GM on PRETXT performance did not

reach significance (R^2 = 0.14, β =0.37, t(25) = 2, p = 0.056) (Table 4, Figure 10). This relationship between brain anatomy and PRETXT performance was present only in the active group, as in the sham group alone the relationships between test performance and CSF (R^2 = 0.07, β =-0.08, t(23) = -0.41, p = 0.683) (Figure 9), GM (R^2 < 0.01, β =0.11, t(23) = 0.05, p = 0.958) (Figure 10), and WM (R^2 = 0.01, β =0.11, t(23) = 0.53, p = 0.6) (Figure 11) were flat. Lastly, in those who received active stimulation, the main effect of electric field magnitude underneath the electrode was significant in predicting PRETXT test performance (R^2 = 0.2, β =0.44, t(23) = 2.48, p = 0.02) (Table 5, Figure 12), with greater electric field magnitude associated with better performance. Underneath the electrode, those in the active group had an average electric field magnitude of 0.16 V/m (SD = 0.04).

Discussion

The results of the current study provide strong evidence for the impact that brain anatomy has on the potential benefits of tDCS. Greater electric field magnitude underneath the electrode predicted better performance, where an increase of 1 SD or 0.037 V/m equated to a 7.5% increase in categorization accuracy. The findings from the current study join a small but growing body of literature exploring the relationship between electric fields calculated via FEM and behavioral outcomes. In the first study to demonstrate such a relationship, current density in the PFC was positively correlated with improvement in a working memory task in a sample of young adults (Kim et al., 2014). Further evidence for this result was provided by a meta-analysis that looked at working memory studies applying tDCS to the PFC and found that performance was related to electric field strength in the PFC (Wischnewski et al., 2021). This relationship between higher current density/electric field

magnitude and behavioral response has also been previously shown in older adults when applying tDCS to the PFC (Albizu et al., 2020). In the current study, the average electric field magnitude underneath the electrode at MNI coordinates 28, 23, 14 in those who received active stimulation was 0.16 V/m, a finding that is in line with the range of 0.10 – 0.40 V/m typically observed for stimulation between 1 and 2 mA (Esmaeilpour et al., 2018; Francis et al., 2003; X. Liu et al., 2019). Using an above chance cutoff for accuracy in the test blocks of 60.5% (Gibson et al., 2021), the difference in electric field magnitude among those in the active group who did and those who did not learn the task is notable, with those 9 subjects above the cutoff having an electric field magnitude of 0.191 V/m (SD = 0.04), and those 18 subjects below the cutoff at 0.149 V/m (SD = 0.03), a significant difference ($p = 0.026$).

Beyond electric field magnitude, lower CSF and a higher WM ratio were also significant predictors of performance in those who received active anodal stimulation, with a higher GM ratio approaching statistical significance. In all three of these cases the interaction between brain anatomy and stimulation is apparent, where significant or nearly significant relationships between brain ratio and performance in the active group can be contrasted with the complete lack of any relationship in the sham group (Figures 9-11). While other attributes like gyri morphology are known to affect current flow (Salvador et al., 2010), this is only the second study to date to find a relationship between general brain anatomy in older adults and tDCS induced behavior change. The one previous study to find such a relationship is one of the few prospective FEM studies in the literature, where modeling was conducted prior to the intervention and used for individual placement of tDCS on the PFC (Rasmussen et al., 2021). Replicating that result in the current study implies near optimal tDCS targeting across a

number of subjects, which is noteworthy given that this montage was originally designed for application in a younger sample (Clark et al., 2012), and it is common for younger and older adults to display different patterns of activation when performing the same task (Davis et al., 2012; Manenti et al., 2011; Reuter-Lorenz & Cappell, 2008; Vallesi et al., 2011).

The relationship between anatomy and performance observed in the current study makes sense given the location of stimulation in the PFC, an area prone to volume changes in aging. This is true for both GM (Sowell et al., 2004) and WM (Barrick et al., 2010; Sullivan et al., 2010). White matter hyperintensities also occur first in anterior regions (Storsve et al., 2016), and have an effect on observed current in FEM studies, reducing flow to nearby non-lesioned areas by up to 7% while also contributing to decreases in overall brain volume (Indahlastari, Albizu, et al., 2021). It is possible that stimulation in posterior regions less prone to atrophy may not evince such a strong relationship between anatomy and performance. In that case precise gyri location may play more of a factor, though electrode placement would need to be very precise across participants, and gyri morphology may only be relevant for the application of so called high definition tDCS (Antonenko et al., 2021; Hill et al., 2018). Aligning with this interpretation, when applied to the sensorimotor cortex during a proprioceptive task, there was no observed correlation between modeled electric field magnitude and performance in older adults (Muffel et al., 2019).

The finding of a significant relationship between WM ratio and age, where WM ratio displayed a sharp decline with age in our sample, was contrary to the hypothesized

relationship. The positive significant relationship between GM ratio and electric field magnitude was also contrary to the hypothesized relationship. The basis for these hypotheses was a previous FEM study, where in a very large sample of 587 older adults, the authors observed the relationship between white matter ratio and age to be very slightly positive (R^2 = 0.007), with increasing WM ratio with age (Indahlastari et al., 2020). They also observed the relationship between GM ratio and current density to be very slightly negative, with decreases in GM ratio explaining only 0.008 % of the variance in current density. However, in the current sample, age was a strong negative predictor of WM ratio (R^2 = 0.39), and GM ratio was a strong positive predictor of electric field magnitude underneath the electrode (R^2 = 0.33). There are several possible reasons for this difference. First, Indahlstari and colleagues used the median current density across several brain regions when an F3-F4 montage was applied, rather than electric field magnitude in a specific location underneath the electrode. While the relationship between current density and electric field magnitude is assumed to be linear, taking the median current density or electric field magnitude across several regions could lead to different results, especially if some of those areas have less atrophy than the rIFG. Second, the inclusion of T-2 and T-1 weighted images in the current study, compared to only T-1 in Indahlstari et al. might be another reason. Including T-2 images has been shown to improve the accuracy of FEM models, including those created in ROAST (Nielsen et al., 2018; Puonti et al., 2020), the program also used by Indahlstari and colleagues. The observed similarity between models with both T-1 and T-2 and models with T-1 were 76% in CSF and 87% in bone (Hoornweder et al., 2022). These differences, coupled with a 92% overlap in WM segmentation, may explain the disparate result seen in the current study, where age explained 55.2% of the variance in brain volume compared to

11.6% in Indahlstari et al. Some of this difference may also be driven by the inclusion of those with MCI in the current study, whom accounted for 27.3% of the total sample. However, with these subjects removed, age still explains 38.4% of the variance in brain volume. The reduction in WM with age seen in the current study is also more in line with the literature generally, where both cross-sectional (H. Liu et al., 2016) and longitudinal (Hedman et al., 2012) studies find that WM volume peaks at around age 50, with decreases accelerating after the age of 60. While increases in CSF have been previously emphasized in FEM studies, findings here indicate that WM and GM volume is also critical for tDCS effect in older adults (Laakso et al., 2015; Mahdavi & Towhidkhah, 2018b; Opitz et al., 2015).

Limitations

There are several limitations to note when interpreting the results of the current study. Including both those with MCI and HC subjects in the same sample is a potential issue for interpretation, yet it is unknown how many of those we classified as MCI based solely on their MOCA score (8 of 15 of those with MCI in the current sample) would actually be classified as such by a neuropsychologist. However, it is noteworthy that differences on the MOCA alone were sufficient to demark those with significant differences in atrophy, lending some credence to the policy of noting those with MOCA scores under 26 as having MCI for the purposes of this study. Even with this policy, there were only 8 MCI subjects in the active group, not enough to analyze separately.

Another potential limitation is differences in electrode placement in actual practice and in FEM. All subjects were modeled with identical idealized placement, but this is unlikely to have occurred in reality. Even small drifts of 5% (around 1-1.5 cm) can significantly alter the results of FEM in electrode placement, changing observed current intensities up to 38% (Opitz et al., 2018; Woods et al., 2015). In practice, online tDCS, where neurons engaged in a specific task and close to firing threshold are said to be preferentially affected by tDCS current (in comparison to unengaged neurons that are not close to their firing threshold), likely mitigates some of the variance seen in small shifts of the electrode (Bikson & Rahman, 2013; Dayan et al., 2013; Miniussi et al., 2013), but there is undoubtedly a point where electrode drift becomes an issue even in online tDCS. Also, models only included electrode placement on the nape of the neck, but placement on the arm may lead to different current flow. Additionally, tissue in the neck was modeled uniformly as skin, but various types of tissues have different conductivities that could have affected currents as they exited the skull.

While FEM provides an avenue for understanding how broad anatomy affects tDCS, it has a significant shortcoming, specifically that it is incapable of accounting for what occurs in an active brain. An important feature in tDCS study design is whether tDCS is applied online during a task, or offline while the subject is not tasked with doing anything specific (Antal et al., 2007; Bortoletto et al., 2015). This difference is important because tDCS is a subthreshold neuromodulator, unable to make neurons fire on its own (Kronberg et al., 2019). Thus what those neurons are doing as tDCS is applied is vitally important to the effect of tDCS. Viewing the brain as passive when it comes to applying tDCS is known theoretically as a stimulation-dependent account, an account that sees the influences of tDCS

as consisting of the inhibitory influence of cathodal stimulation, the excitatory influence of active stimulation, and the placement of these two types of stimulation on the body. Of course the brain is not passive, but rather contains a currently unfathomable amount of moving parts. How these myriad parts interact with tDCS is something that is not fully understood and is unable to be accounted for in FEM.

It is challenging to even gauge how much of a problem this is for the accuracy of FEM. As previously stated, neurons close to firing threshold are preferentially engaged by tDCS, engendering a targeted effect in task specific networks in online stimulation. Given this, in a particular task it is possible that areas in the brain connected to a location receiving current themselves undergo important downstream effects via structural connectivity, even if that secondary location is not receiving any current directly. In contrast there may be an area far from the electrode where a FEM model finds significant current, but in that case a beneficial tDCS effect in this area that contributes towards task performance cannot be assumed. Equating places receiving current according to FEM with places getting an effect from tDCS is an assumption that must be tested separately for each task and each brain region (Jones et al., 2021), because as a whole the FEM literature does not provide evidence that areas of significant current flow not directly underneath the electrode are actually meaningful for the tDCS effect in any given task (Hunold et al., 2022).

Future Directions

To address these limitations, more work is necessary to explicate the utility of FEM models. Since few studies using forward FEM models have been performed, the accuracy of their predictions has not been widely tested. To date, only one study has successfully used prospective individualized FEM to guide tDCS placement (Rasmussen et al., 2021). The results of this study were promising, but future studies should directly compare FEM-individualized montages and one-size-fits-all montages to understand the benefit of FEM. The existing ratio of prospective to retrospective FEM studies is potentially problematic, and possibly indicative of unpublished null results, in which case more null results of FEM models should be published. With more of these gaps filled, it may become clear that FEM is more useful in specific instances, such as when modeling precise application of high definition-tDCS, modeling offline stimulation, or modeling current path in older adults. In older adults, calculating dosage based on FEM is promising and may be a way of ameliorating variability in tDCS effect among those in a given sample of older adults. For example, it was calculated that currents up to 3.25 mA would be needed in some older adults to reach the current equivalent of 2 mA in younger adults (Indahlastari et al., 2020).

However, the current finding that anatomy itself quantified by WM, GM, and CSF ratio is predictive of tDCS effect means that FEM models of tDCS current flow might not be necessary, especially where tDCS is applied to areas that typically have the most age-associated atrophy, like the PFC. In the current study, electric field magnitude explained 20% of the variance in performance, compared to CSF ratio at 21% and WM ratio at 22%. Combined into one model, WM, GM and CSF together explained 25% of the variance in performance. Such an equation accounting for these three variables could potentially be used

to personalize current dose, and in that instance it is not clear what is added by performing FEM of current flow. That brain anatomy has not often been predictive of tDCS effect previously may be due to the commonality of using only T1 weighted imaging for segmentation instead of the combination of T1 and T2 used in the current study. Indeed, the one study to identify a relationship between brain anatomy in the form of cortical thickness and tDCS-mediated performance improvements used a combination of T-1 and T-2 weighted images for segmentation (Rasmussen et al., 2021). MRI scans themselves might even be made redundant, a potential advantage as one of the chief benefits of tDCS is its low cost, and maintaining that benefit would necessitate the preclusion of expensive individual MRIs. An alternative would be to establish a likely relationship between brain anatomy and transcranial magnetic stimulation motor-evoked potentials, and then use differences in motor-evoked potentials to calculate dosage (Caulfield et al., 2020).

Other factors may serve as moderators in the relationship between anatomy and tDCS-elicited performance gains, because while structural brain changes often coincide with declines in cognitive performance, there is extensive heterogeneity, with some individuals able to marshal compensatory resources in order to maintain cognitive function in the face of inevitable age-related changes (Park & Festini, 2017). The current study did not measure such a compensatory relationship, instead finding that anatomy plays a direct effect on performance. However, compensatory mechanisms may serve as a moderator between changes in anatomy and cognitive performance, and future studies should measure the extent to which factors known to be protective may disrupt the straightforward relationship between anatomy and performance observed in the current study. For example, functional

neuroimaging measures in older adults often display a pattern dedifferentiation, where older adults see less specific task-associated activation patterns compared to younger adults (Hakun et al., 2015b; Reuter-Lorenz & Park, 2010), as well as changes in resting state networks, like decreased functional connectivity within individual networks like the default mode, salience, and central executive/fronto-parietal control network coupled with increased connectivity between these networks (Andrews-Hanna et al., 2007; He et al., 2014). Future studies should examine how connectivity changes impact the application of tDCS and subsequent task performance.

Conclusion

This study provides a mix of both expected and novel findings. Among findings with a good deal of previous empirical support, this study observed that brain anatomy changes with age and that there are discernible differences in anatomy between those with and without MCI. Among more novel findings, this study joins a small literature demonstrating that electric field magnitude and brain anaotmy affect the potential gains of tDCS. Future work needs to further our understanding of the role of FEM can play in mitigating the heterogeneity of and improving outcomes from tDCS application in older adults.

Figures

Figure 1: Project design.

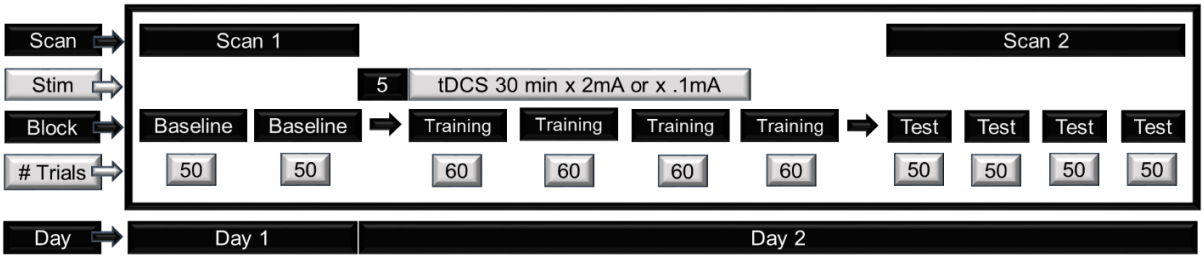


Figure 2: Comparison of CSF, grey matter, and white matter between healthy controls (HC) and subjects with Mild Cognitive Impairment (MCI). Error bars +/- 1 SE.

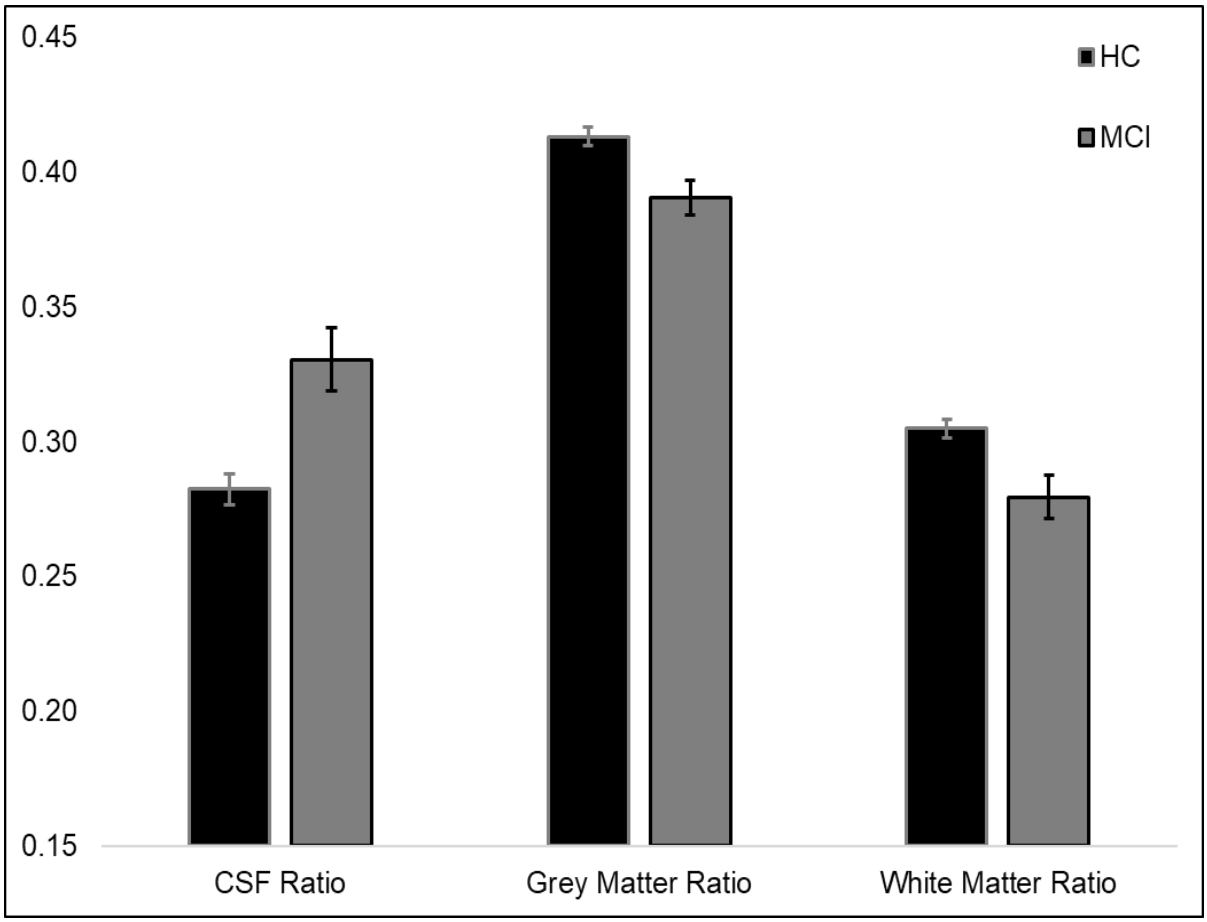


Figure 3: Relationship between age and CSF ratio.

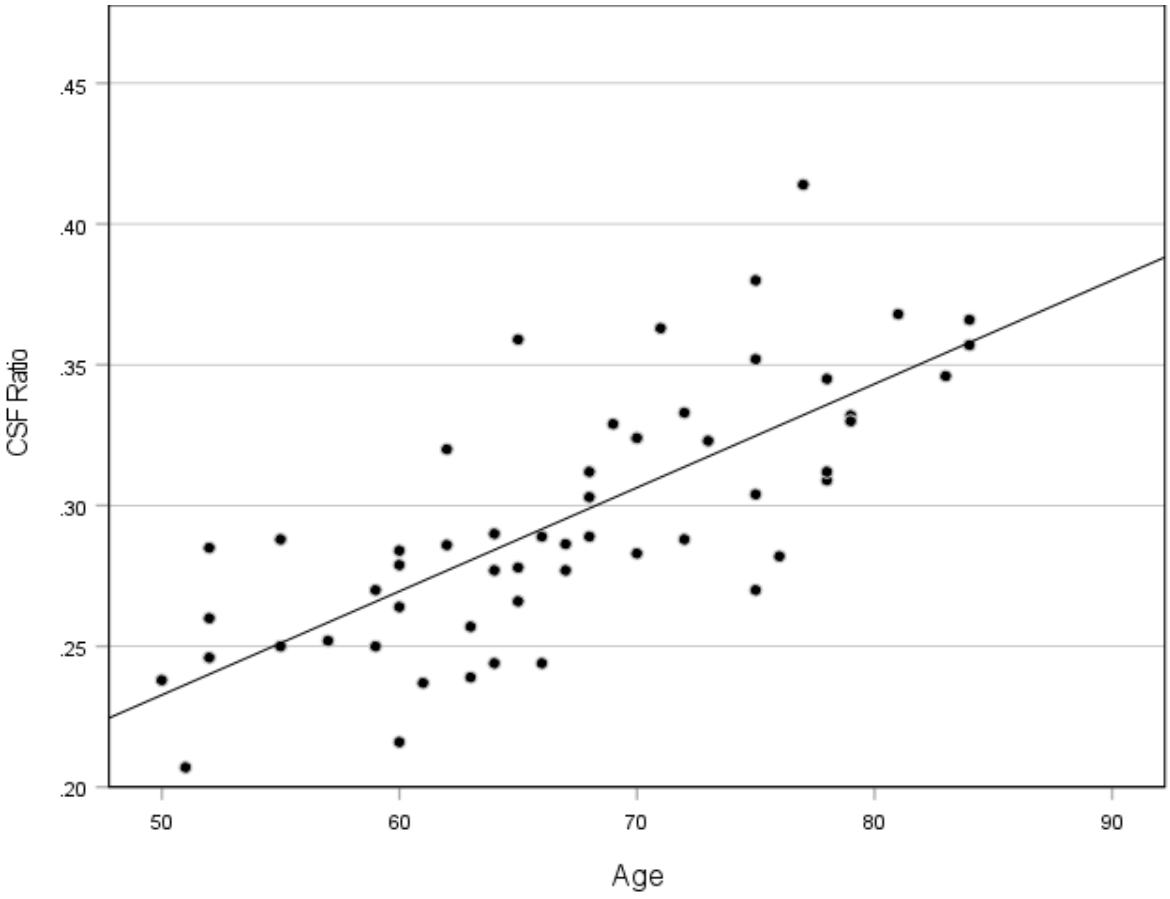


Figure 4: Relationship between age and grey matter ratio.

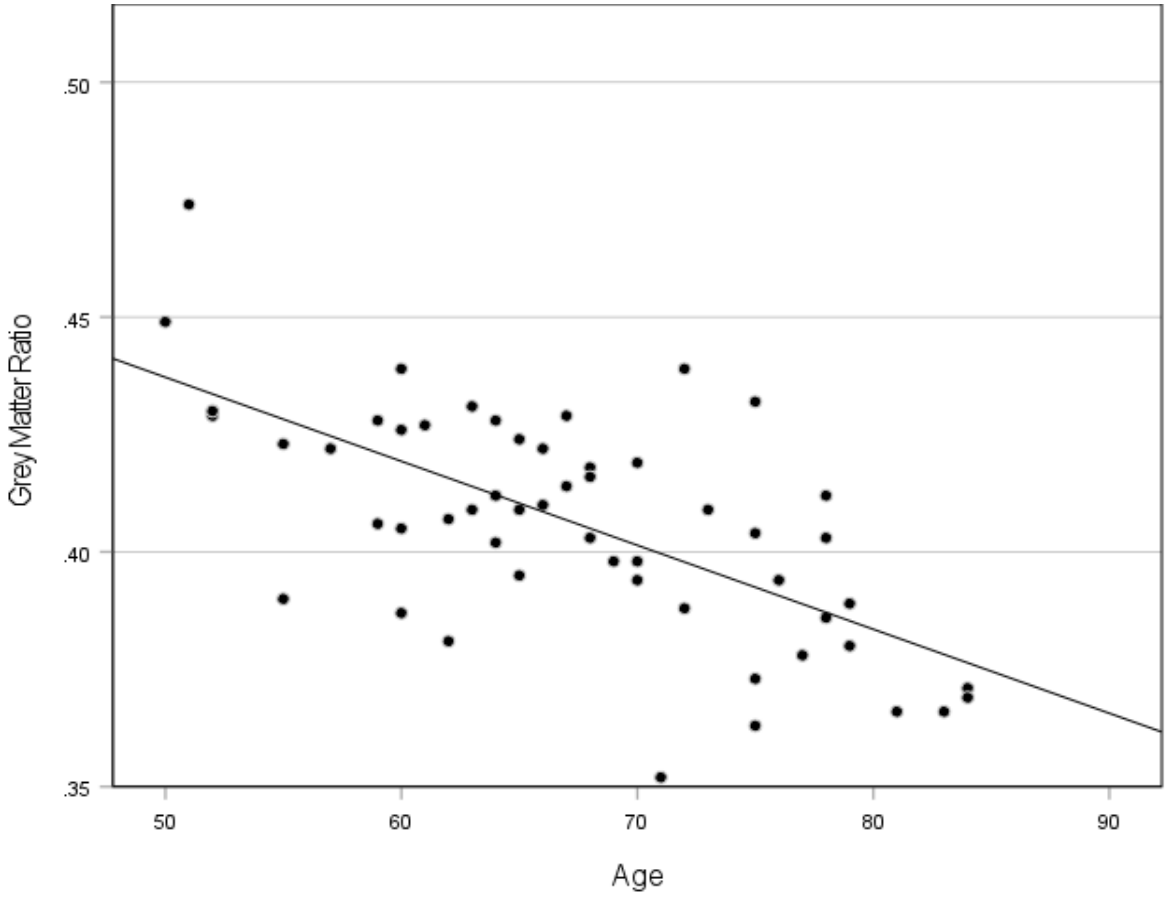


Figure 5: Relationship between age and white matter ratio.

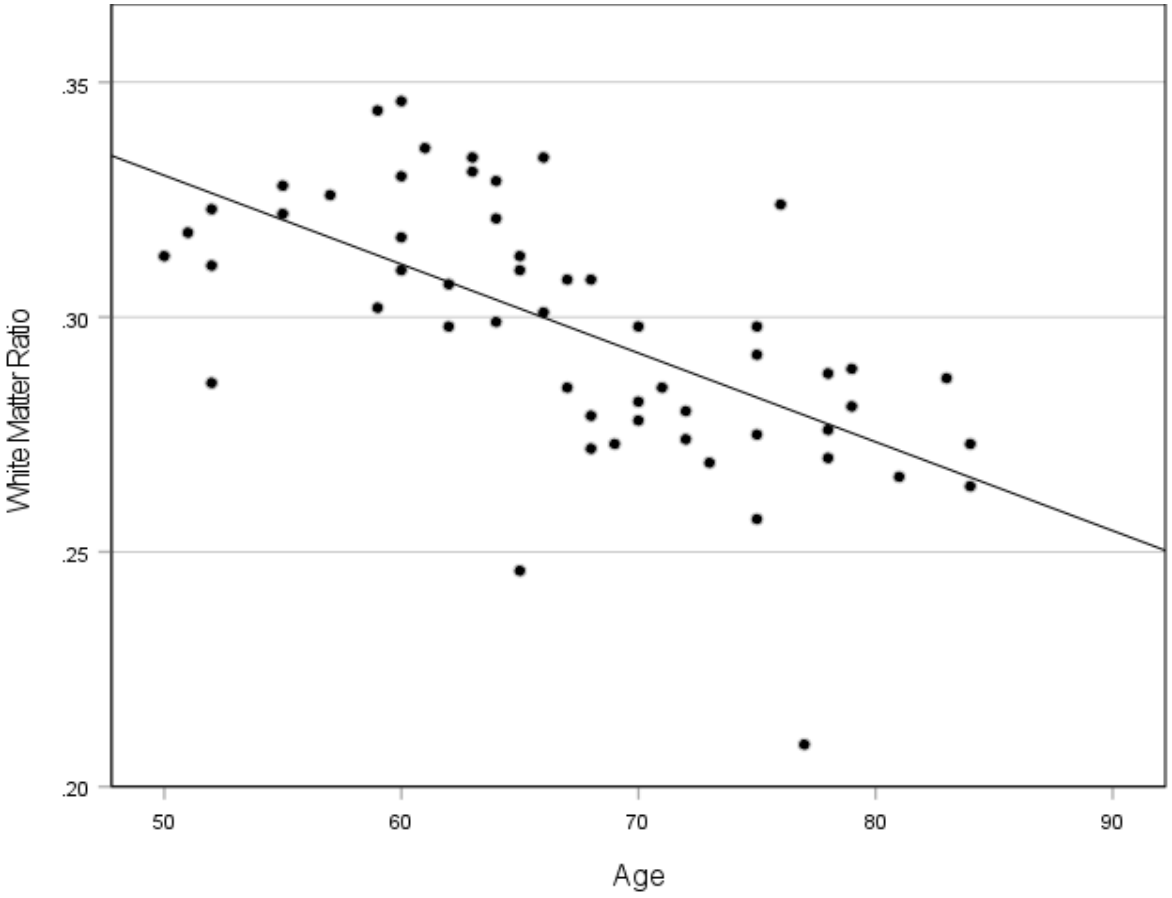


Figure 6: Relationship between CSF ratio and electric field magnitude for those who received active stimulation.

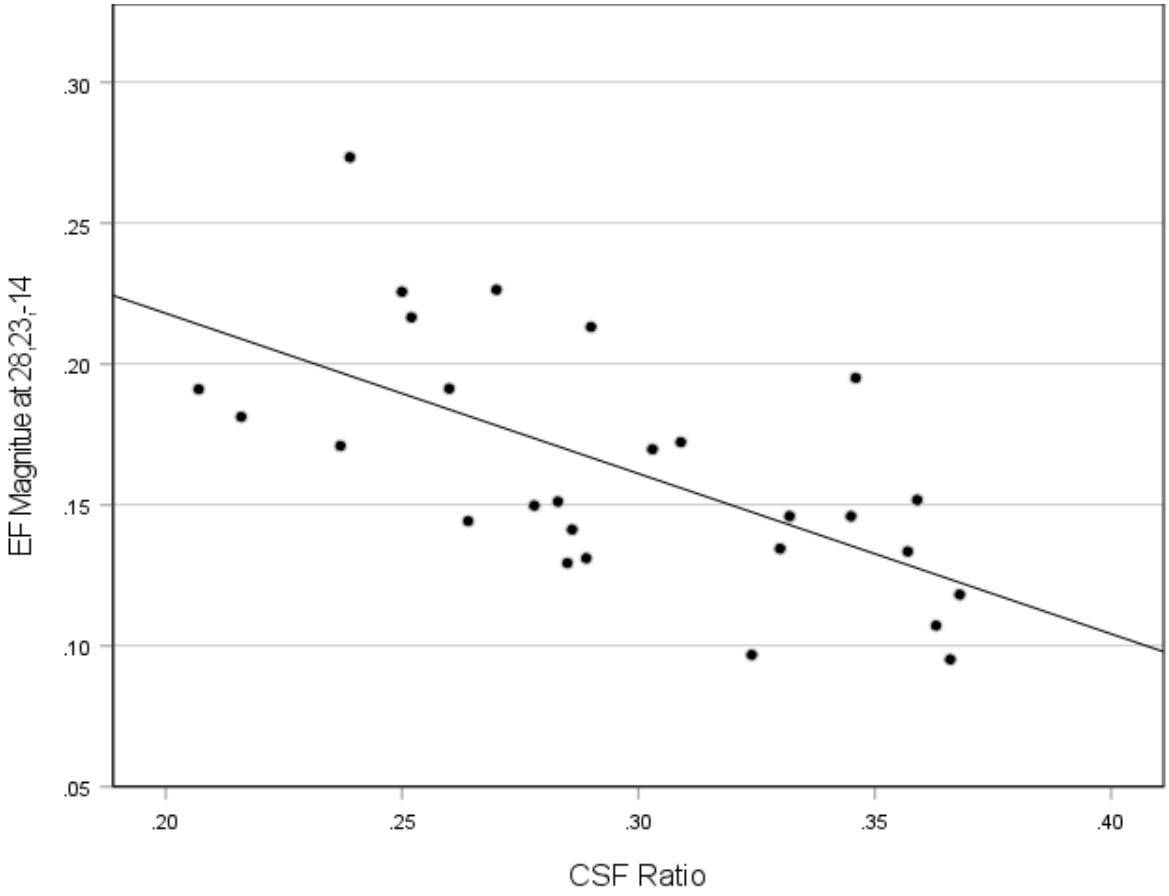


Figure 7: Relationship between grey matter ratio and electric field magnitude for those who received anodal stimulation.

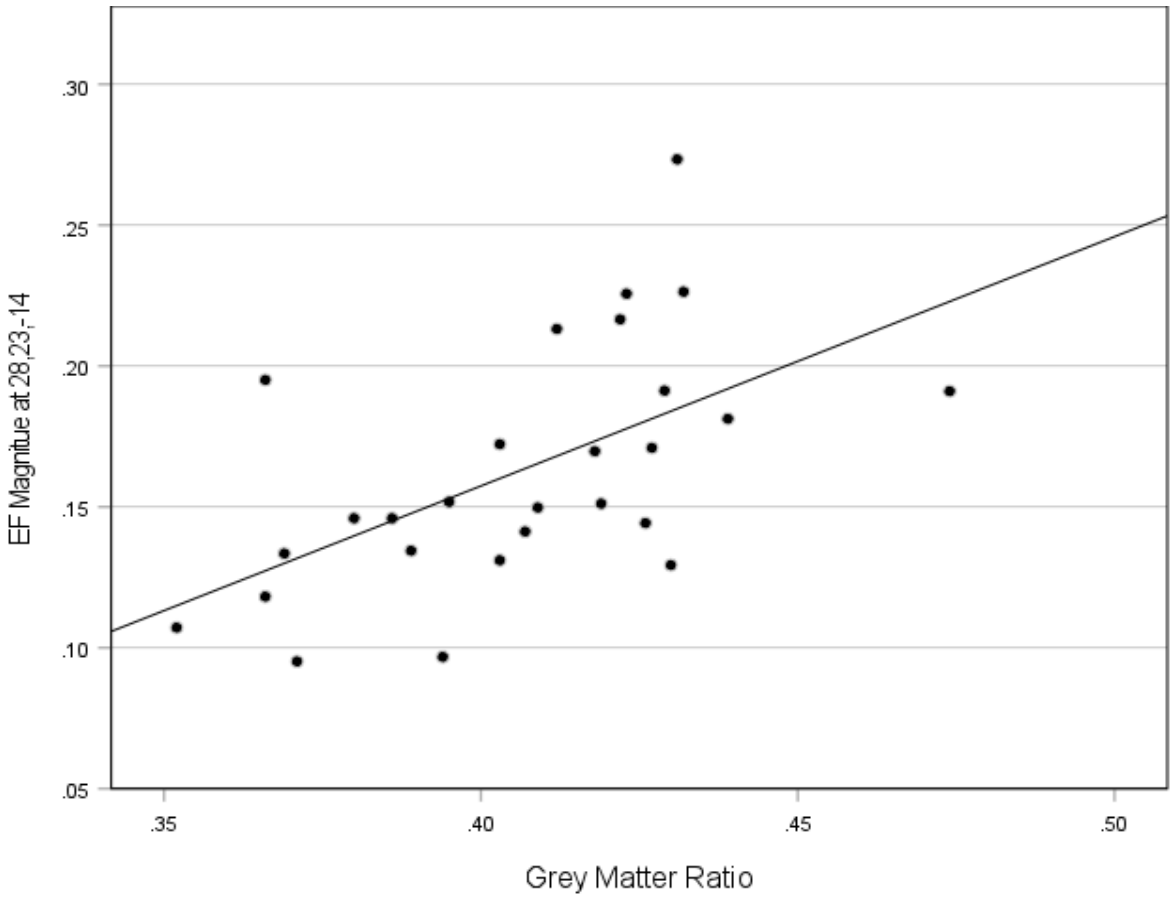


Figure 8: Relationship between white matter ratio and electric field magnitude for those who received active stimulation.

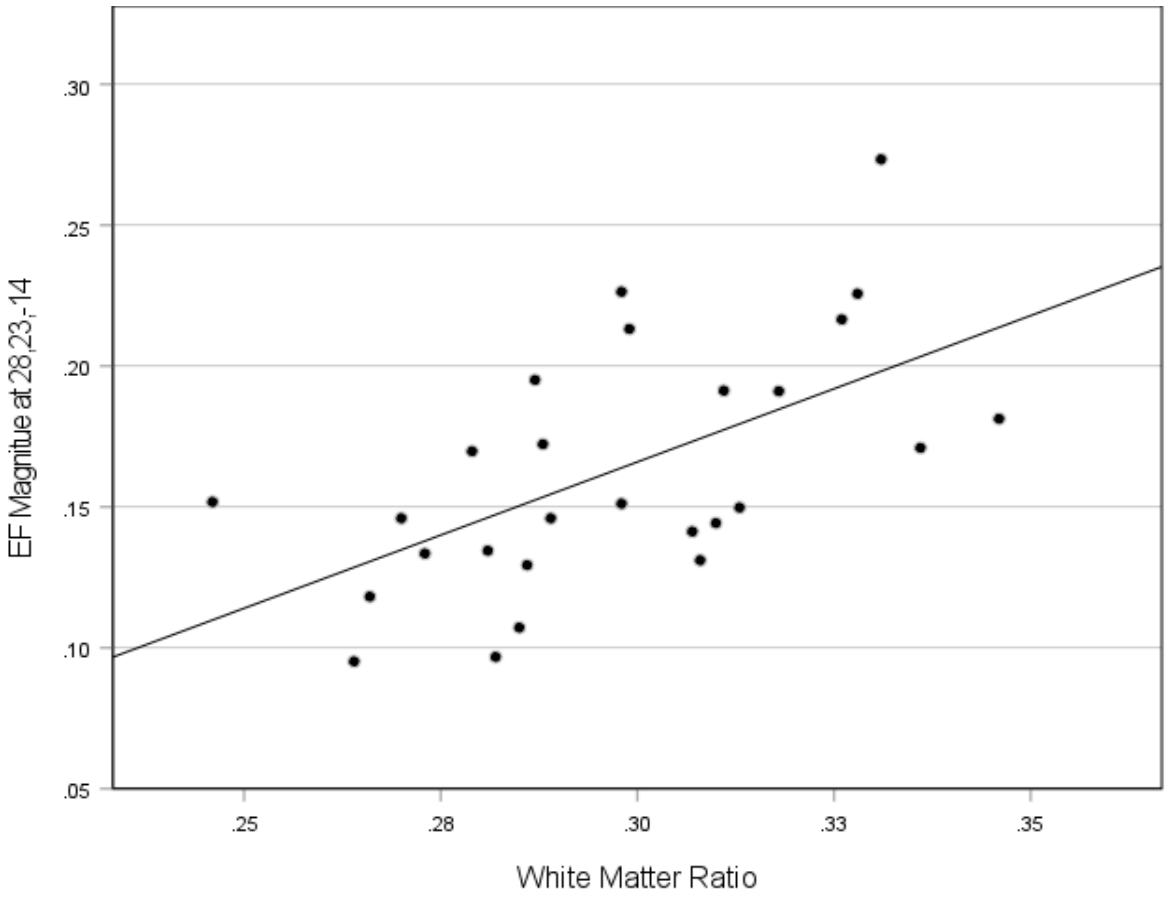


Figure 9: Relationship between CSF ratio and PRETXT test performance for those who received active stimulation.

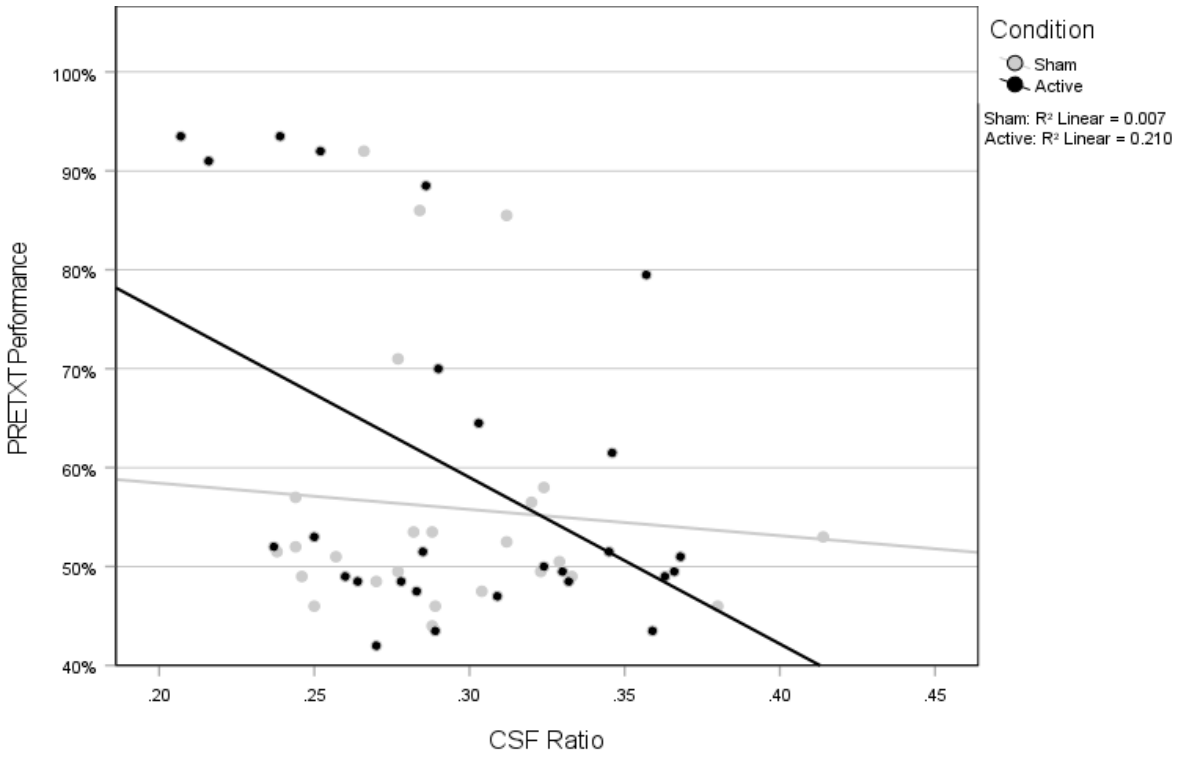


Figure 10: Relationship between grey matter ratio and PRETXT test performance for those who received active stimulation.

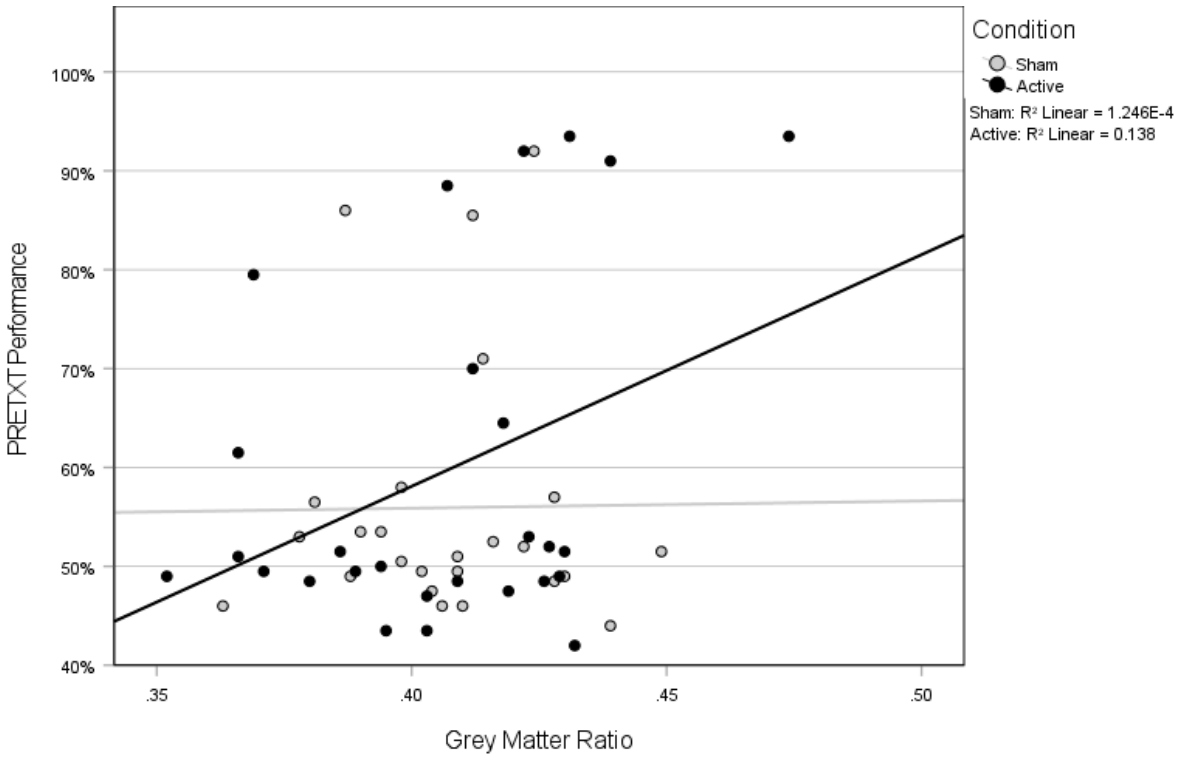


Figure 11: Relationship between white matter ratio and PRETXT test performance for those who received active stimulation.

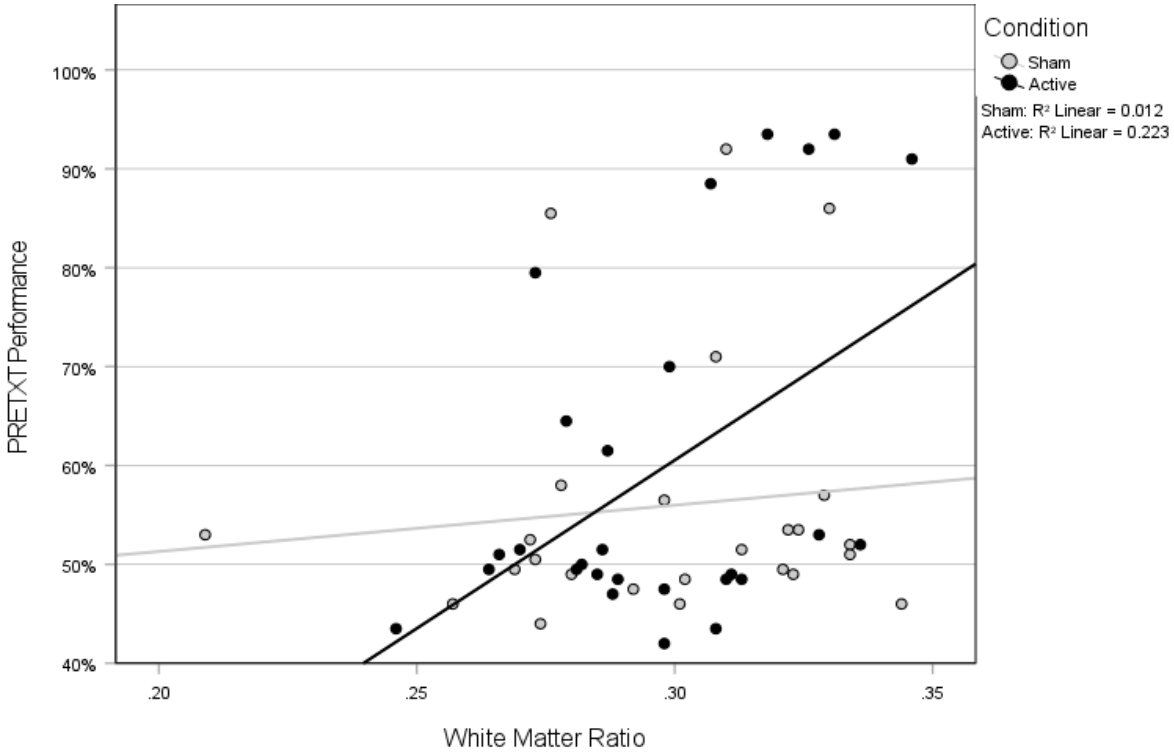
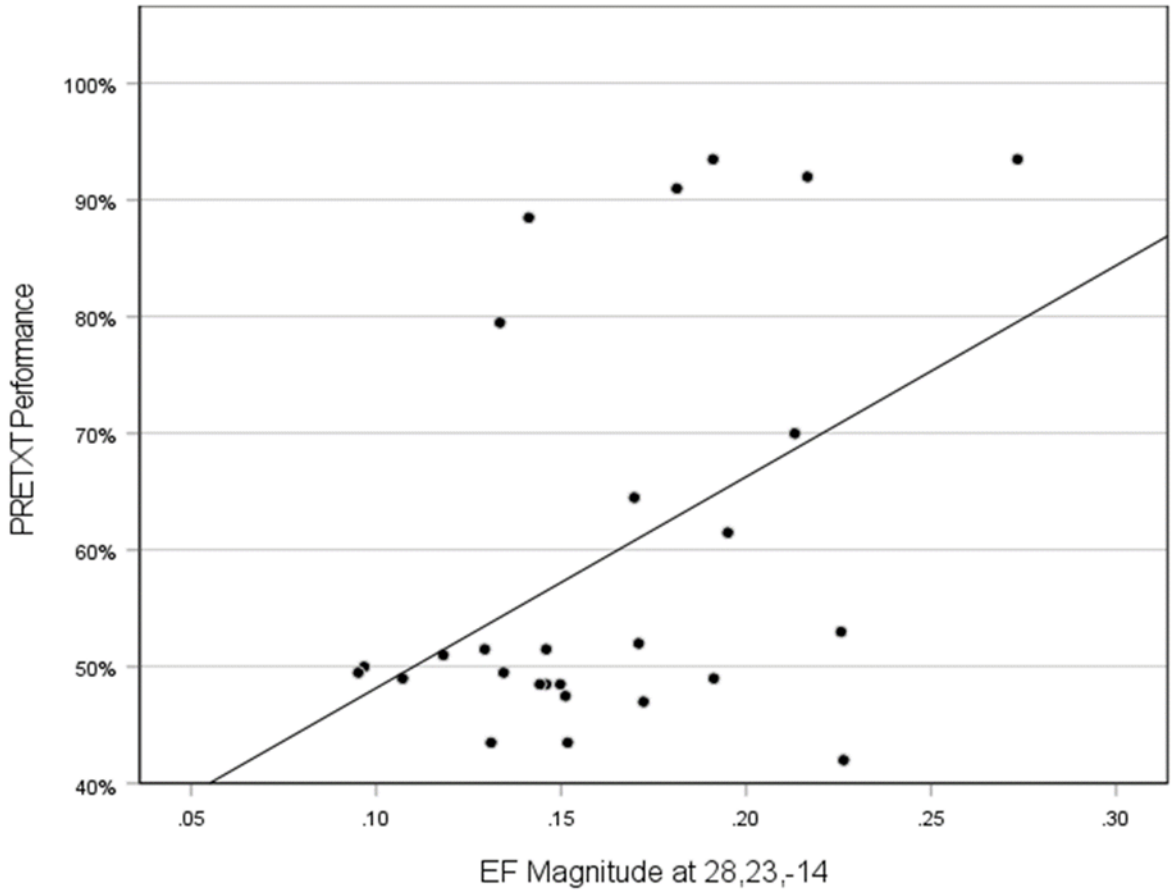


Figure 12: Relationship between electric field magnitude at MNI coordinate 28, 23, -14 and PRETXT test performance for those who received active stimulation.



Tables

Table 1: *Sample Demographics*

	Total (N=55)	Active (n=27)
	Mean (SD) or n (%)	Mean (SD) or n (%)
Age	67.2 (8.9)	67.9 (10.3)
MCI	15 (27.3%)	8 (29.6%)
Male	23 (41.8%)	12 (44.4%)
Black	2 (3.6%)	0 (0%)
Hispanic	10 (18.2%)	3 (11.1%)
Native American	2 (3.6%)	1 (3.7%)
White	41 (74.5%)	23 (85.2%)

Table 2: *Age predicting CSF, Grey Matter, and White Matter Ratios among all subjects*

	Variable	B (SE)	β	t	p	R^2
Model 1	CSF Ratio	0.004 (<.001)	0.74	8.07	< 0.001	0.55
Model 2	Grey Matter Ratio	-0.002 (<.001)	-0.66	-6.45	< 0.001	0.44
Model 3	White Matter Ratio	-0.002 (<.001)	-0.63	-5.84	< 0.001	0.39

Table 3: *CSF, Grey Matter, and White Matter Ratios predicting electric field magnitude in the active group*

	Predictor	B (SE)	β	t	p	R^2
Model 1	CSF Ratio	-0.57 (.14)	-0.63	-4.06	<0.001	0.39
Model 2	Grey Matter Ratio	0.89 (.25)	0.57	3.48	0.002	0.33
Model 3	White Matter Ratio	1.04 (.29)	0.59	3.62	0.001	0.34

Table 4: *CSF, Grey Matter, and White Matter Ratios predicting PRETXT Performance in the active group*

	Predictor	B (SE)	β	t	p	R^2
Model 1	CSF Ratio	-168.27 (65.32)	-0.46	-2.58	0.016	0.21
Model 2	Grey Matter Ratio	234.22 (65.32)	0.37	2	0.056	0.14
Model 3	White Matter Ratio	340.28 (127.19)	0.47	2.68	0.013	0.22

Table 5: *Electric field magnitude predicting PRETXT performance*

Predictor	B (SE)	β	t	p	R^2
EF Magnitude	181.12 (72.93)	0.45	2.48	0.02	0.2

The Interaction between Intra and Inter Network Connectivity and Transcranial Direct Current Stimulation (tDCS) on Category Learning in Older Adults

Abstract

Numerous changes occur in the aging brain. One that is observable during analyses of resting state functional connectivity has been labeled "dedifferentiation," and is characterized by decreases in correlated activity between the nodes of a given network, such as the default mode network (DMN), and increases in correlated activity between the nodes of one network and the nodes of another, such as between the DMN and salience network (SN). These increases in dedifferentiation have been shown to correlate with decreases in cognitive performance. This study aimed to investigate the relationship between dedifferentiation, age, and cognitive performance following the application of transcranial direct current stimulation (tDCS) in a combined sample of healthy older adults and those with mild cognitive impairment (MCI). Consistent with findings of dedifferentiation in older adults, increasing age was associated with stronger internetwork connectivity between the DMN, frontoparietal control network (FPCN), and SN. Additionally, in those who received 2.0 mA of active anodal stimulation over 10-20 site F10 with cathodal stimulation on the left arm for 30 minutes, stronger intraconnectivity in the FPCN network was predictive of better task performance. This result joins a growing body of literature explicating the effects of dedifferentiation in older adults, while at the same time being one of the first studies to describe how tDCS impacts measures of dedifferentiation, and the interaction between tDCS, dedifferentiation, and performance in a learning task.

Introduction

Aging is associated with a decline of cognitive function, a decline that can have a detrimental effects on quality of life (Harada et al., 2013). With an aging population, more remedial methods for combating age-associated cognitive decline are needed (Ortman, 2014). Transcranial direct current stimulation (tDCS), a form of noninvasive brain stimulation, offers a new possibility for combating age related cognitive decline, and there have already been several positive findings from the application of tDCS in healthy older adults. These findings have found improvements in working memory, (Min-Ho et al., 2011; Satorres et al., 2022), executive function (Hanley & Tales, 2019; Šimko et al., 2021), memory consolidation (Perceval et al., 2020), and language function following interventions with tDCS (Matar et al., 2020). Those with mild cognitive impairment (MCI) have also benefited from tDCS application with improvements observed following cognitive training paired with tDCS (Gonzalez et al., 2018; Martin et al., 2019). However, there are also a number of published null results (Kaminski et al., 2017; Leach et al., 2018; Nilsson et al., 2015, 2017), indicating that heterogeneity is a major issue for tDCS application in older adults. This heterogeneity, due to both experimental and individual factors, is still largely unclassified across the tDCS literature, but this is especially the case in older adults (Habich et al., 2020).

One source of heterogeneity in older adults is changes in brain morphology, which can greatly affect tDCS outcomes. On the macroscopic scale, decreases in white matter and grey matter volume, coupled with an increase in cerebrospinal fluid volume, poses a problem for tDCS in older adults as it potentially affects tDCS current flow, both reducing the amount of current that reaches the cortical surface and affecting the flow of current that does reach the

brain (Laakso et al., 2015; Mahdavi & Towhidkhah, 2018; Study 2). On the microscopic scale, additional changes to the structure of neurons, such as the loss of synaptic spines or decreased functionality of the N-methyl-D-aspartate receptor (Magnusson, 2012; Morrison & Baxter, 2012) may affect what designs are possible in older adults, potentially making offline studies, where tDCS is applied prior to a task, less feasible due to the shortened window of long term potentiation changes that may not outlast the application of stimulation (Fertonani et al., 2014).

Functional organization also changes with age, like that measurable by resting state functional magnetic resonance imaging. In that modality, subjects are placed in the scanner and not given a specific task. Often, they are told to keep their eyes open and look at a fixation cross, but otherwise the mind is free to wander. Resting state functional connectivity (rsFC), the measurement that comes from resting state functional magnetic resonance imaging, is the amount of positive or negative correlation between specific brain areas and their respective fluctuations in blood oxygen level dependent measurement during this time without a specific activity. In functional connectivity analyses, areas of simultaneous co-occurring activity are said to be functionally connected. This is in contrast to areas with direct fiber connections which are said to be structurally connected. Structural connectivity is thus a physical relationship, while functional connectivity is a statistical relationship (Buckner et al., 2013; Fox & Raichle, 2007). Patterns in rsFC, resting state networks, resemble those seen in task-based studies, so it is thought they similarly represent the underlying organization of the brain (M. W. Cole et al., 2014; Crossley et al., 2013; Spreng et al., 2010). A feature of rsFC is that it places minimal demands on the subject other than the

need to keep still, making it easier to standardize since it does not involve the presentation of stimuli. This is advantageous in populations like older adults who may have difficulty performing tasks within the scanner (Study 1). Despite the seeming simplicity, however, the examination of rsFC data is starting to yield clinically useful data (E. J. Cole et al., 2021), and a number of resting state networks have been identified, including the executive or fronto-parietal control network (FPCN), dorsal attention or task-positive network, ventral attention or salience network (SN), sensorimotor network, visual network, and task-negative or default mode network (DMN) (Smitha et al., 2017; Varangis et al., 2019).

In older adults, specific patterns are visible in rsFC where older adults display increased inter-network connectivity and decreased intra-network connectivity (Antonenko & Flöel, 2014; Damoiseaux, 2017; Deery et al., 2023; Sala-Llonch et al., 2015; Vieira et al., 2020). This fits into a general pattern of "dedifferentiation", "demodularization", or “desegregation” that occurs in the aging brain, where in task based fMRI, specific activation patterns seen in younger adults become increasingly less pronounced with age (Park & Reuter-Lorenz, 2009a). Reductions in intra-network connectivity mean that in the absence of a task the nodes of the DMN, such as the posterior cingulate cortex, medial prefrontal cortex, and angular gyrus, display reduced functional connectivity to each other. However, they exhibit more functional connectivity to the nodes of other networks, like the dorsolateral prefrontal cortex and posterior parietal cortex of the FPCN (Allen et al., 2011; Grady et al., 2016; Spreng et al., 2016; Tomasi & Volkow, 2012). Such dedifferentiation has been observed in both cross-sectional studies comparing older adults to younger adults (Ferreira et al., 2016; Geerligs et al., 2015; Hrybouski et al., 2021), and longitudinal studies following older adults over time

(Chong et al., 2019; Ng et al., 2016; Zonneveld et al., 2019). The amount of change seen in various networks also varies in the aging brain, with some like the visual network experiencing little change; others like the limbic network demonstrating an increase in segregation from other networks (Andrews-Hanna et al., 2007; Hrybouski et al., 2021; Malagurski et al., 2020); and others like the SN, FPCN, and DMN experiencing greater change that follows the dedifferentiation pattern (Schulz et al., 2022).

Changes visible in rsFC in older adults are also associated with cognitive performance. These include changes in connections within networks, such as studies that found stronger FPCN intraconnectivity related to better working memory and verbal memory (Geerligs et al., 2015; Stumme et al., 2020), and studies that found stronger DMN intraconnectivity related to better episodic memory (Fjell et al., 2015) and processing speed (Staffaroni et al., 2018). And changes in connections between networks, like where overall desegregation of the DMN, FPCN, SN, and other networks from one another was associated with worse episodic memory (Chan et al., 2014), worse processing speed (Varangis et al., 2019), and worse attention (Chong 2019). Also, stronger internetwork connectivity between the FPCN and DMN specifically was correlated with worse associative memory (Grady et al., 2016) and worse verbal memory (Stumme et al., 2020). In a study that followed adults over the age of 65 for 4 years, a decrease in segregation of different networks was seen over that period, with the SN, DMN, and FPCN having the strongest declines. Additionally, reductions in the segregation of the FPCN over that time correlated with a decline in processing speed. When controlling for age, the effect of desegregation of the FPCN was still significant, indicating that rsFC is predicative of cognitive performance even when the effects of age are accounted

for (Malagurski et al., 2020). Separating age from rsFC is important, because while it is expected that changes in rsFC will correlate with increasing age, to justify their use, measures of rsFC must have additional utility beyond age and the other brain changes, such as decreases in grey matter and white matter, and increases in cerebrospinal fluid (Study 2) that also correlate with age. Besides being correlated to cognitive performance, rsFC has also been predictive of improvement following cognitive interventions. Less dedifferentiation of the FPCN, DMN, SN, as well as others at baseline was associated with greater executive function improvement following a 6 month exercise regimen (Baniqued et al., 2018), (Gallen et al., 2016). In another study, lower baseline connectivity between the nodes of the SN and other networks was also related to better learning (Iordan et al., 2018).

Only two studies have used measures of rsFC prior to tDCS application to explore differences in who might benefit the most from tDCS, one of which was in healthy older adults. In the other study with younger adults, those with higher baseline connectivity within the DMN had better gains after 5 days of working memory training coupled with tDCS application to the left dorsolateral prefrontal cortex (Cerreta et al., 2020). In the study with older adults, those with lower baseline connectivity between the FPCN, dorsal attention network, and sensorimotor network had larger improvements in visual working memory during the application of tDCS to the left dorsolateral prefrontal cortex (Pupíková et al., 2022). Changes in rsFC have been observed following tDCS application in older adults, with some studies noting that tDCS changed rsFC patterns in older adults, making them more similar to those of younger adults (Antonenko et al., 2019; Lindenberg et al., 2013; Meinzer et al., 2013; Nissim, O'Shea, Indahlastari, Telles, et al., 2019; J. Zhou et al., 2020).

The current study builds on these previous findings by further exploring the relationship between age and dedifferentiation, and more importantly, whether patterns of rsFC visible in older adults prior to tDCS application can be used to predict the benefits of tDCS.

Methods

This study recruited healthy older adults and those with mild cognitive impairment (MCI) to investigate the effects of tDCS on cognitive performance and brain function. The participants were required to be right-handed, aged between 50-90 years, English speakers before the age of 7, and without a history of neurological or psychiatric disorders. They additionally were excluded for excessive drug or alcohol use, epilepsy, migraines, stroke, traumatic brain injury, other chronic illnesses, or current COVID-19 symptoms. Potential participants needed to be inexperienced with tDCS and be able to receive an MRI. Healthy control subjects were not allowed to be taking medications with possible psychotropic effects, but participants with MCI were allowed to be taking these medications. Subjects with MCI needed to be able to sign a consent form, or have a legally authorized representative able to sign on their behalf. Both those who came with an existing diagnosis of MCI as well as those who scored a 26 or lower on the Montreal Cognitive Assessment (MOCA) were classified as having MCI for this study.

The study consisted of two days of participation (Figure 1). On day one subjects completed the resting state scan as well as the baseline portion of the cognitive task, the Predicting Response To F10(X) tDCS) or PRETXT task, while in the scanner. The PRETXT task was

performed immediately before the resting state scan. Please see Study 1 and Study 2 for further description of the PRETXT task. On day two, tDCS was applied during the training portion of the PRETXT task followed by an additional scan where the test portion of the PRETXT task was performed in the scanner, and again it was followed by the resting state scan. tDCS was applied using an ActivaDose II iontophoresis unit and delivered 2 mA of anodal stimulation for 30 minutes to the right inferior frontal gyrus, or F10 on the international 10/20 system, with the cathode placed on the contralateral triceps. The current was delivered using sponges soaked in SignaGel that were placed in a rubber holder with a metal backing during application. For double-blinding, two ActivaDose units were connected to a blinding box with 6 switches, half of which allowed the current from the ActivaDose machine administering the active dose of 2.0 mA to pass, while the other half allowed the current from the ActivaDose machine administering the sham dose of 0.1 mA to pass.

Magnetic Resonance Imaging Parameters

Participants were scanned with a 3T Prisma system with 32 channel head coil (Siemens; Erlangen, Germany). The parameters for the T-1 weighted structural image were: repetition time [TR] = 2500 milliseconds; echo time [TE] = 1.81, 3.6, 5.39, 7.18 milliseconds; inversion time [TI] = 1000 milliseconds; flip angle = 8 degrees; number of excitations [NEX] = 1; slice thickness = 0.8 mm; field of view (FOV) 256 mm; matrix size = 320x320; voxel size 0.8 mm cubed). For the T-2 acquisition the parameters were repetition time [TR] = 3200 milliseconds; echo time [TE] = 564 milliseconds; flip angle = 8 degrees; number of excitations [NEX] = 1; slice thickness = 0.8 mm; field of view (FOV) 256 mm; matrix size = 320x320; voxel size 0.8 mm cubed). Resting state data was acquired over a 10-minute period

using a single-shot, gradient-echo planar pulse sequence (TR = 800 milliseconds; TE = 37 milliseconds; flip angle = 52 degrees; multiband acceleration factor = 8; NEX = 1; slice thickness = 2 mm; FOV = 208mm; matrix size 104x104) with 72 interleaved 2-mm slices acquired for whole brain coverage (voxel size: 2x3mm). A total of 738 images were collected.

Resting State Data Processing

Image processing was done in CONN Toolbox. Functional volumes were realigned and unwarped to account for subject motion estimation and correction with a subject motion threshold of .9 mm. Slice timing correction was performed and outlier scans above 97th percentile were identified and removed. Grey matter, white matter, and cerebrospinal fluid volumes were segmented and normalized in MNI space and the skull was stripped. Data was denoised using component-based noise correction, the anatomical component-based noise correction, and the global signal regression before being band-pass filtered for frequencies below 0.008 and above 0.09 Hz. Linear detrending was performed along with despiking before regression. Regions of interest (ROIs) for the DMN, SN, and FPCN networks were defined using the Network Atlas in CONN. The ROIs for the DMN were the medial prefrontal cortex, left and right angular gyri, and posterior cingulate cortex. For the SN, they were the anterior cingulate cortex, left and right anterior insula, left and right anterior prefrontal cortex, and left and right supramarginal gyri. Lastly for the FPCN network the ROIs were left and right dorsolateral prefrontal cortices and left and right posterior parietal cortices. Please see Figure 2 for visual representation of the ROIs (Chabran et al., 2020)

Statistical Analysis and Hypotheses

Mean time series were extracted from each ROI, and Pearson correlation coefficients were calculated for all possible pairs of ROIs within and between the networks of interest. The correlation coefficients were Fisher transformed in CONN toolbox to improve normality and these were used in individual regression analyses (Hausman 2020) and one-way ANOVAs. Statistical analyses were conducted in Statistical Product and Service Solutions (SPSS). Eight regression analyses were performed in SPSS, four exploring the relationship between connectivity and age and four exploring the relationship between connectivity and performance on the PRETXT task. For both outcomes, the four connectivity measures of interest were intra-network connectivity in the DMN, SN, and FPCN networks, and average inter-network connectivity between these three networks. Finally, 4 one-way ANOVAs were conducted to explore any possible differences in intra-network and average inter-network connectivity between those classified as healthy controls and those classified as having MCI.

Hypotheses for the models were the following:

1) With increasing age there will be decreasing strength in intra-network connectivity within the DMN, FPCN, and SN.

2) With increasing age, there will be increasing inter-network connectivity, marked by increases in positive correlations and decreases in anticorrelations between these three networks.

3) In addition, stronger intra-network connectivity in the DMN, FPCN, and SN will predict better task performance in those who receive active tDCS.

4) Weaker inter-network connectivity between these networks will predict better task performance in those who receive active tDCS.

Results

Subjects

Fifty-four subjects had baseline rsFC collected. One was excluded for having missing PRETXT data, leaving 53 subjects. The average age was 67.1 (*SD* = 8.92) years. Most of the sample identified as female, 30 or 56.6%, and as non-Hispanic white, 38 or 71.7%. Twenty-seven subjects were included in the active tDCS group, where likewise the majority identified as female, 15 or 55.6%, and non-Hispanic white, 23 or 85.2%. Fifteen subjects (28.3%) in the sample were classified as having MCI, including 8 or 29.6% of those who received active stimulation. See Table 1 for complete demographic information.

Age and connectivity

In the models exploring the relationship between age and rsFC, age was not a significant predictor of intraconnectivity in the DMN (R^2 = 0.03, β = -0.17, $t(52)$ = -1.25, p = 0.217) (Figure 3), FPCN (R^2 = 0.06, β = -0.25, $t(52)$ = -1.82, p = 0.07) (Figure 4), or SN (R^2 = 0.01, β = -0.7, $t(53)$ = -0.5, p = 0.616) (Figure 5). However, age was a significant predictor of internetwork connectivity (R^2 = 0.08, β = 0.27, $t(52)$ = 2.05, p = 0.046), accounting for 8% of the variance where increasing age was associated with increasing average connectivity between the DMN, FPCN, and SN (Figure 6). This average difference was driven by stronger

internetwork connectivity between the DMN and SN (R^2 = 0.08, β = 0.28, t(53) = 2.05, p = 0.045) and between the FPCN and SN (R^2 = 0.11, β = 0.32, t(52) = 2.45, p = 0.018), while no relationship was found between age and connectivity between the DMN and FPCN (R^2 = 0.001, β = 0.04, t(52) = 0.25, p = 0.8). Please see Table 2 for the statistics of the age and connectivity models.

Connectivity and performance

Among those who received active stimulation, neither intraconnectivity within the DMN (R^2 = 0.05, β = 0.21, t(26) = 1.08, p = 0.289) (Figure 7) or SN (R^2 = 0.03, β = 0.21, t(26) = 1.08, p = 0.289) (Figure 8) was predictive of PRETXT performance. In contrast, intraconnectivity in the FPCN network predicted a statistically significant 20% of the variance in task performance in the active group, with stronger connectivity in the FPCN network associated with better PRETXT performance (R^2 = 0.2, β = 0.45, t(26) = 2.48, p = 0.020) (Figure 9). Average connectivity between the DMN, FPCN, and SN was not associated with task performance in the active group (R^2 = 0.07, β = -0.26, t(26) = -1.36, p = 0.185) (Figure 10). Among the relationships between these networks, only the relationship between the SN and FPCN was predictive of performance among those who received active stimulation (R^2 = 0.11, β = -0.38, t(26) = -2.11, p = 0.046), with connectivity between the SN and DMN (R^2 = 0.08, β = -0.33, t(26) = -1.75, p = 0.092) and DMN and FPCN (R^2 = 0.01, β = 0.11, t(26) = 0.53, p = 0.603) not predictive of performance. In those who received sham stimulation, intraconnectivity within the DMN (R^2 = 0.10, β = 0.31, t(25) = 1.59, p = 0.125) and FPCN (R^2 < 0.001, β = -0.01, t(25) = -0.037, p = 0.971) was not significantly associated with performance, but interconnectivity in the SN was a significant predictor of performance (R^2 =

0.18, β = 0.43, $t(25) = 2.3$, $p = 0.030$). For internetwork connectivity among those who received sham stimulation, average internetwork connectivity ($R^2 = 0.11$, β = -0.32, $t(25) = -1.68$, $p = 0.106$), connectivity between the DMN and FPCN ($R^2 = 0.006$, β = -0.08, $t(25) = -0.388$, $p = 0.701$), and connectivity between the SN and FPCN ($R^2 = 0.05$, β = -0.22, $t(25) = -1.09$, $p = 0.125$) were not significant predictors of performance. In contrast, connectivity between the DMN and SN was predictive of performance ($R^2 = 0.17$, β = -0.41, $t(25) = -1.21$, $p = 0.037$).

Differences between those with MCI and healthy controls

Four separate one-way ANOVA's were conducted to explore differences in intra and inter network connectivity between those classified in the MCI group and those classified as HC (Figure 11). None of these differences were significant, though differences in intraconnectivity in the DMN ($F(1,52) = 3.63$, $p = 0.062$), FPCN ($F(1,52) = 3.48$, $p = 0.068$), and SN ($F(1,52) = 3.49$, $p = 0.067$) were approaching significance, where in all three between groups comparisons healthy controls had stronger within network connectivity. Average connectivity between the DMN, FPCN, and SN was also not significantly different between healthy controls and those classified as having MCI ($F(1,52) = 0.56$, $p = 0.458$), and none of the relationships between these networks approached significance. (Figure 10).

Discussion

The current study is one of the first to find that differences in rsFC can predict performance following the application of active anodal tDCS. Specifically, stronger intraconnectivity in

the FPCN predicted better performance in the active anodal group. Interpreting the β from that analysis, a one standard deviation increase in the positive strength of the correlation coefficient (approximately $r = 0.19$) equated to a 7.5% increase in categorization accuracy in the PRETXT task. Given that the average improvement in categorization accuracy in the active group over the course of the task was 11.5%, the predictive power of FPCN intranetwork connectivity is quite large. Differences in rsFC according to age were also observed, with a trend towards dedifferentiation consistent with the literature, though in the current sample only the change in average inter-network connectivity between the DMN, FPCN, and SN reached significance, where a one SD increase in age, 8.9 years, resulted in an increase in the average correlation between these networks of $r = 0.035$.

Post-hoc tests revealed that the significant change in inter-network connectivity with age (Figure 5), was driven entirely by the SN, both its relationship with the DMN and the FPCN. In contrast, no relationship was observed between age and connectivity between the DMN and FPCN. The SN is thought to play a role in switching between the task negative DMN and task positive FPCN in order to efficiently use attention and working memory (Uddin, 2015). Individuals with stronger segregation between the SN and FPCN networks have also shown better performance on tests of executive function and attention, suggesting that the ability to flexibly switch between these two networks is an important aspect of cognitive control (Seeley et al., 2007). The result in the current study joins others that demark the SN as a nexus of age associated change (Meier et al., 2012), especially the relationship between the SN and other networks, such as the DMN, where desegregation has been observed in longitudinal and cross sectional studies (Ferreira et al., 2016; Malagurski et al., 2020).

Compared to young adults, nodes in the SN of older adults have more connections to nodes in other networks (Iordan et al., 2018), and connectivity of the SN and DMN was best able to differentiate older and younger adults in a machine learning study (La Corte et al., 2016). In that same study, SN connectivity was better able to predict cognitive performance in older adults than age itself, meaning there is utility for rsFC over and above age (La Corte et al., 2016). Indeed, this was also the case in the current study, where increasing age was also an inferior predictor of cognitive performance ($p = 0.192$) across the entire sample in comparison to internetwork connectivity of the SN. Other studies have found the DMN to be important in older adults, both its connection to the FPCN and its within network connections (Grady et al., 2016; Ng et al., 2016), but neither was found to be associated with age or task performance in the current study. The current results are consistent with the older adults' rsFC literature, however, where different networks emerge in different studies. On the whole there is strong support for the dedifferentiation hypothesis in older adults, with a recent meta-analysis finding decreased within-network connectivity in 37 of 50 studies and increased between-network connectivity in 32 of 37 studies (Deery et al., 2023).

Also revealed by post-hoc tests, the relationship between the SN and FPCN was related to performance, where those with weaker correlations between the nodes of the SN and the FPCN performed better after active stimulation. The SN is particularly relevant to the PRETXT task, where subjects are tasked with learning an arbitrary rule to correctly classify European streets into 2 categories, and the SN is thought to be involved in the detection of pertinent stimuli and the monitoring of rules (Han et al., 2019; Sestieri et al., 2014). Thus,

subjects with weaker segregation of the SN may have been less able to filter out irrelevant information.

A previous study applying active tDCS to the same target as the current study, the right inferior frontal gyrus (rIFG), found that stimulation altered the relationship between the SN and DMN, strengthening deactivation of the DMN with concurrent SN activation (Li et al., 2019). Activation of the right anterior insula, a critical SN structure, is correlated with concurrent DMN deactivation and better cognitive control. (Hampshire and Sharp 2015; Touroutoglou 2012) The right anterior insula is functionally connected to the rIFG during tasks (Aron et al., 2014; Hampshire et al., 2010; Sridharan et al., 2008; Touroutoglou et al., 2012), and is thought to be stimulated when tDCS is applied to the rIFG (Hunter et al., 2015; Li et al., 2019). In contrast, application of tDCS to the dorsolateral prefrontal cortex has been shown to affect connectivity within the FPCN (Peña-Gómez et al., 2012). It is thus possible that rIFG stimulation can affect the relationship between the SN and DMN, but not the relationship between the SN and FPCN, so that the health of the SN and FPCN inter-network connectivity which subjects have before tDCS application affects their performance. This interpretation is supported by findings in the sham group, where instead, SN and DMN inter-network connectivity was predictive of performance.

This possibility is supported further by connectivity within the FPCN, which was found to be a significant predictor of performance in those who received active stimulation with larger positive correlations between FPCN nodes associated with better task performance (Figure

8). The FPCN is a task positive network associated with cognitive performance, such as that which occurs during working memory and goal directed attention (Hausman et al., 2022; Palva et al., 2010). The FPCN also underlies the adaption to feedback (Dosenbach et al., 2007). Given that the PRETXT task requires discovery learning, where subjects must learn to separate pictures into two categories through iterative hypothesis testing and feedback, this is a critically important function. In one of only two previous studies that used rsFC to predict tDCS effects, Cerreta et al. explored whether rsFC within the DMN and FPCN could predict outcomes following tDCS mediated working memory training in young adults (Cerreta et al., 2020). They found that intraconnectivity in the DMN, and not the FPCN, predicted tDCS benefit, the opposite of the current study. These results fit in with an interpretation that sees the stimulation of the dorsolateral prefrontal cortex, the target in the Cerreta study, as a direct way to affect FPCN intranetwork connectivity, an effect not accomplished by right IFG stimulation. This interpretation is further supported by studies that have applied anodal tDCS to the dorsolateral prefrontal cortex and observed increased connectivity within the FPCN following stimulation (Nissim, O'Shea, Indahlastari, Kraft, et al., 2019; J. Zhou et al., 2020).

The results from the current study bear on the implications of dedifferentiation in older adults. While the relationships observable in rsFC of older adults, weaker intra-network connectivity and stronger inter-network connectivity, are a critical part of the literature and evidence for dedifferentiation, this theory was proposed following observations in task-based blood oxygen level dependent (BOLD) fMRI. There, in comparison to younger adults, older adults who performed as well as younger adults sometimes did so while displaying comparatively larger amounts of BOLD activation (Hakun et al., 2015b; Reuter-Lorenz &

Cappell, 2008; Reuter-Lorenz & Park, 2010). This is especially true during tasks requiring executive function and the prefrontal cortex, where in some cases tasks that are accompanied by unilateral prefrontal cortex activation in younger adults are accompanied by bilateral activation in adults with a similar performance level (Davis et al., 2012; Turner & Spreng, 2012b). In cases where greater BOLD in older adults has correlated with performance equaling that of younger adults with less BOLD activation, dedifferentiation has been proposed as a form of compensation, where older adults need to marshal more neurological resources to maintain a high level of cognitive performance (Cabeza & Dennis, 2013; Park & Reuter-Lorenz, 2009b) In cases where greater BOLD is not associated with better performance, dedifferentiation is better interpreted as representing age-related decline in the specialization of specific brain regions and increased inefficiency in neural processing, such as in cases where bilateral prefrontal cortex recruitment was associated with worse performance (Goh, 2011; Meinzer et al., 2009; Stern, 2009). Findings from the current study support the latter interpretation, where dedifferentiation is only associated with worse performance in older adults. In this it concurs with the majority of studies exploring the rsFC correlates of cognitive performance in older adults (Chan et al., 2014; Chong et al., 2019; Geerligs et al., 2015; Grady et al., 2016; Stumme et al., 2020; Varangis et al., 2019). It is also noteworthy that less dedifferentiation, specifically within the FPCN, predicted the benefits of tDCS. This is a conceptual departure from the finding frequently observed in tDCS studies where poorer performers benefit more from tDCS application (Krebs et al., 2021; Perceval et al., 2020; D. Zhou et al., 2015), and perhaps evidence of a disconnect between anatomical and physiological measures associated with poor performance and poor performance itself in older adults.

Limitations

The inclusion of both healthy controls and those with MCI in the current study is a potential limitation. However, no significant differences in connectivity patterns were found between healthy controls and those with MCI in the current study, though these differences may have emerged with a larger sample size. Importantly, the main results of the study still hold if those with MCI are removed, with age still predictive of average internetwork connectivity in healthy controls ($p = 0.046$), and FPCN intra-network connectivity still predictive of task performance ($p = 0.04$) in those who received active stimulation.

Sample sizes larger than 53 are preferred for imaging studies, but the current study had a sample size comparable to others that have examined imaging correlates of tDCS (Li et al., 2019; Peña-Gómez et al., 2012; Polanía et al., 2011). Also, for examining how age affects rsFC, cross-sectional analyses like the current study can observe differences across those of different ages, but only longitudinal studies can observe changes in rsFC that occur with age. Longitudinal studies do mirror cross-sectional studies in older adults in supporting network dedifferentiation (Staffaroni et al., 2018; Zonneveld et al., 2019), but increased nuance can be observed in longitudinal studies, such as the finding that while segregation within the FPCN and DMN continues to decline into old age, segregation of the salience network within individuals decreases until around age 75, and slightly increases thereafter (Malagurski et al., 2020). Undoubtedly, greater insights would be garnered from collecting rsFC measures and correlating these with performance across time. Finally, while earlier criticisms of the utility

of rsFC in understanding the brain have largely been drowned out by the sheer amount of rsFC findings that have accumulated in the intervening years, it is still useful to remember the limitations of rsFC and acknowledge that "rest" does not hold a privileged place when it comes to understanding the brain (Buckner et al., 2013; Finn, 2021; Gal et al., 2022; Morcom & Fletcher, 2007). Given this, it is also possible, perhaps likely, that there are better ways to predict the effects of tDCS besides rsFC (Study 2).

Future Directions

Future work should look at changes in rsFC following stimulation, and changes in FC during PRETXT task performance, in order explicate the relationships observed here. Specifically, it was observed that those displaying less dedifferentiation between the SN and FPCN, and within the FPCN, benefited more from active stimulation, with the same pattern seen between dedifferentiation, aging, and cognitive performance. As discussed previously, however, it is possible that the relationship between existing functionally of the FPCN and PRETXT task performance is due to the stimulation site, where the rIFG provides a way to more readily affect SN activity and not FPCN activity. Stimulating the right dorsolateral prefrontal cortex, rather than the rIFG, may then offer a method to improve FPCN connectivity, and by extension PRETXT task performance, directly. However, before stimulation is applied elsewhere, the changes in connectivity following the current protocol should be examined. In that case it is tDCS induced reductions in dedifferentiation within the SN that would be expected to correlate with better performance.

Imaging modalities measuring effective rather than functional connectivity may also provide a method of predicting tDCS response following application to the rIFG. For example, in one study, fractional anisotropy, a measure of white matter health, within the SN predicted response to tDCS of the rIFG. Those with low fractional anisotropy had no improvement with active stimulation (Li et al., 2019). Similarly, in another study more voluminous white matter tracts leading from the rIFG predicted the effects of cathodal stimulation of that same location on improvements in picture naming speed (Rosso et al., 2014). Studies like these performed in older adults may offer a way of understanding important differences behind disparate tDCS findings in younger and older adults. Ultimately, however, the goal of work combining tDCS and imaging should be to glean what insights are possible from imaging, but not devise protocols that make tDCS application dependent on neuroimaging. Much work remains to be done to understand the substantial heterogeneity inherent in tDCS application, and for this neuroimaging will undoubtedly play a part, but the ultimate advantages of tDCS is that it is comparatively simple to implement, inexpensive to procure, and exceptionally safe to use. Techniques which impinge upon the cost/benefit ratio of tDCS should not be a part of long-term programs for tDCS implementation.

Conclusion

The current study found that differences in rsFC can predict performance following the application of active anodal tDCS, where stronger intraconnectivity in the FPCN predicted better performance in the active anodal group. Differences in rsFC with age were also observed, consistent with findings of dedifferentation. These findings highlight the potential predictive power of rsFC in understanding the effects of tDCS and emphasize the importance

of studying the relationship between different brain networks and how they interact with cognitive interventions.

Figures

Figure 1: Project design.

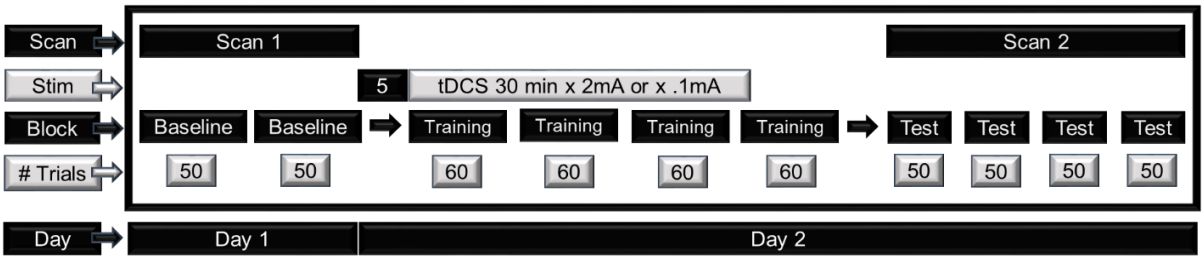


Figure 1: Regions of interest in the current study. Taken from Chabran et al., 2020.

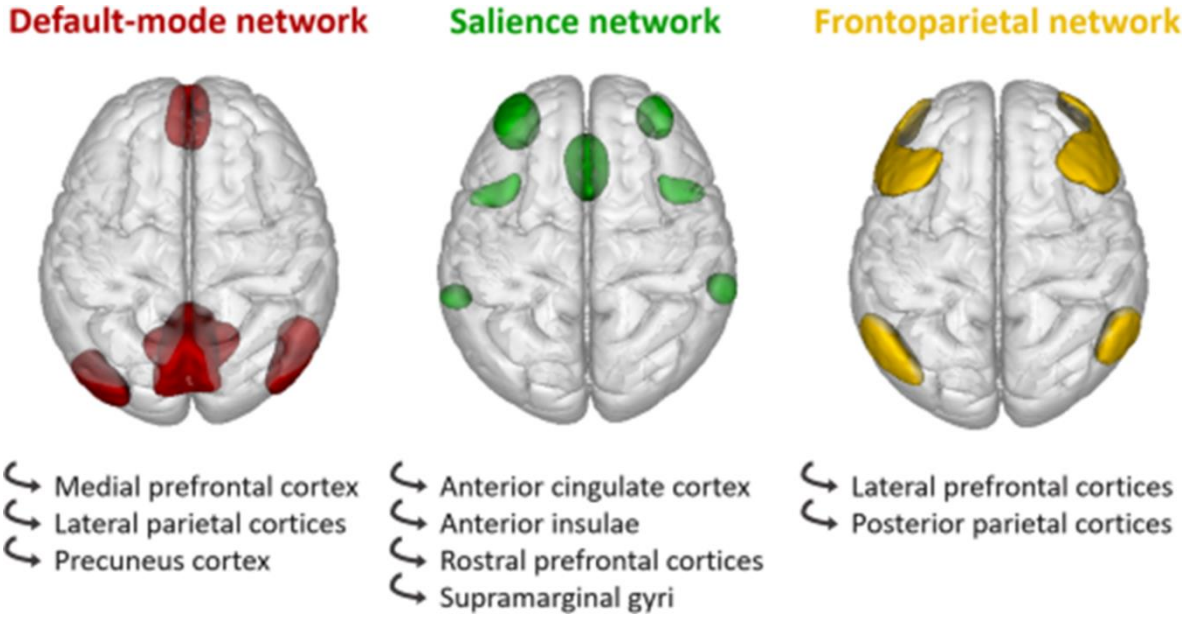


Figure 3: Relationship between age and intra-network connectivity in the default mode network, represented in unstandardized correlation coefficients.

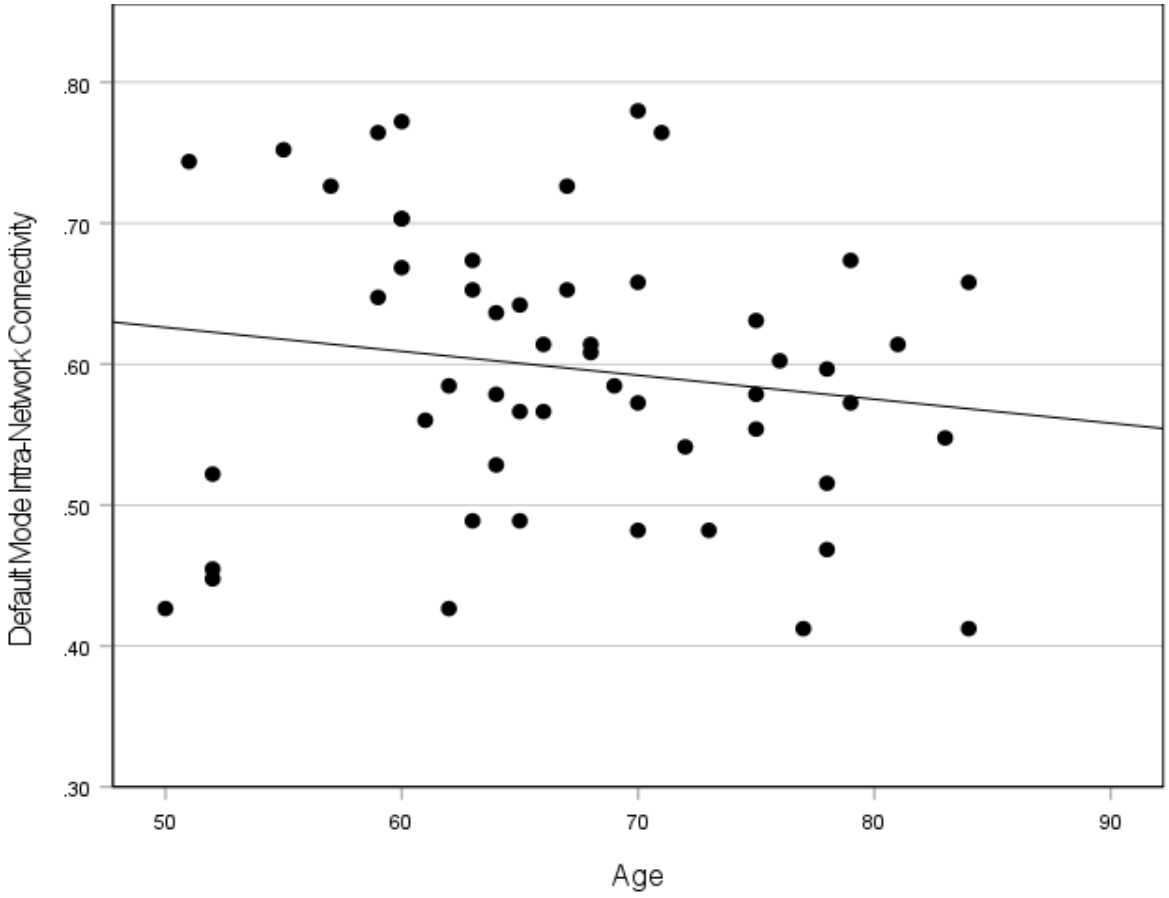


Figure 4: Relationship between age and intra-network connectivity in the fronto-parietal control network, represented in unstandardized correlation coefficients.

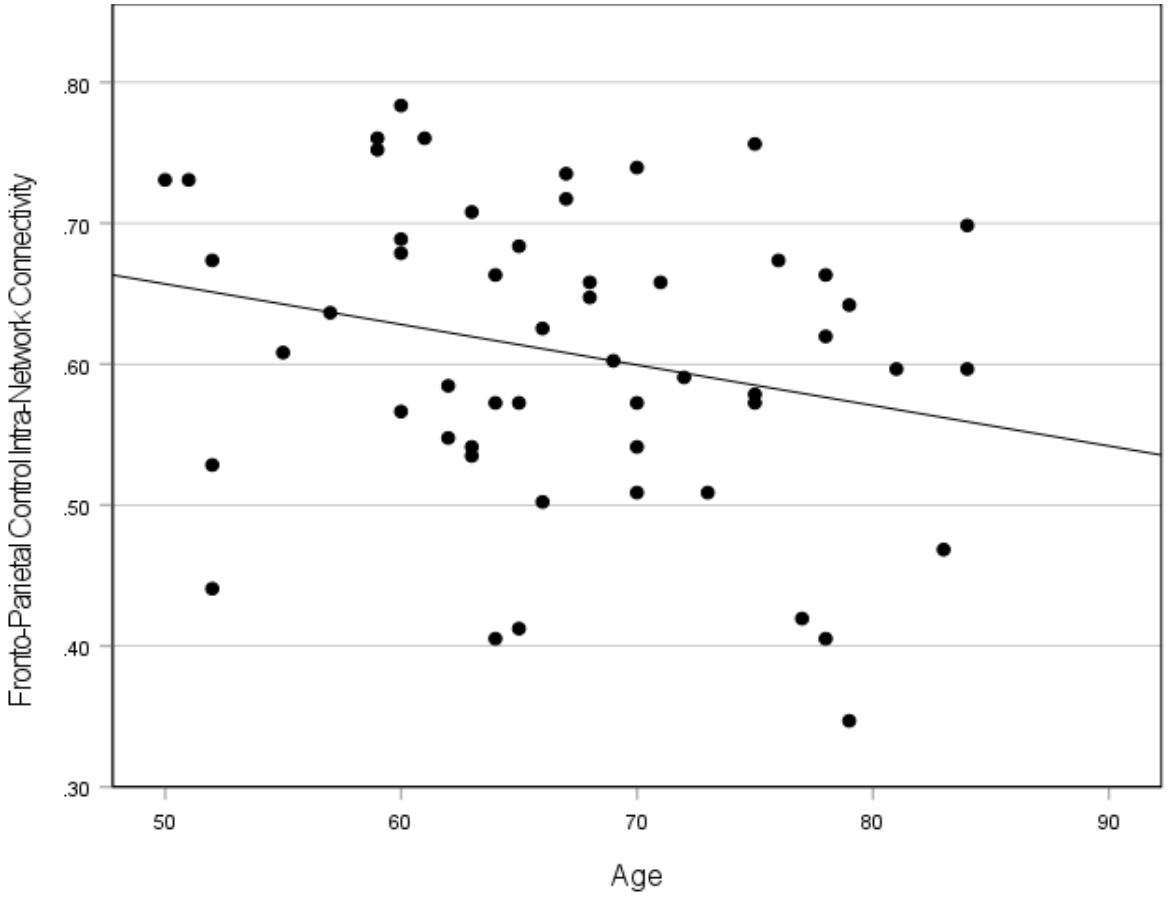


Figure 5: Relationship between age and intra-network connectivity in the salience network, represented in unstandardized correlation coefficients.

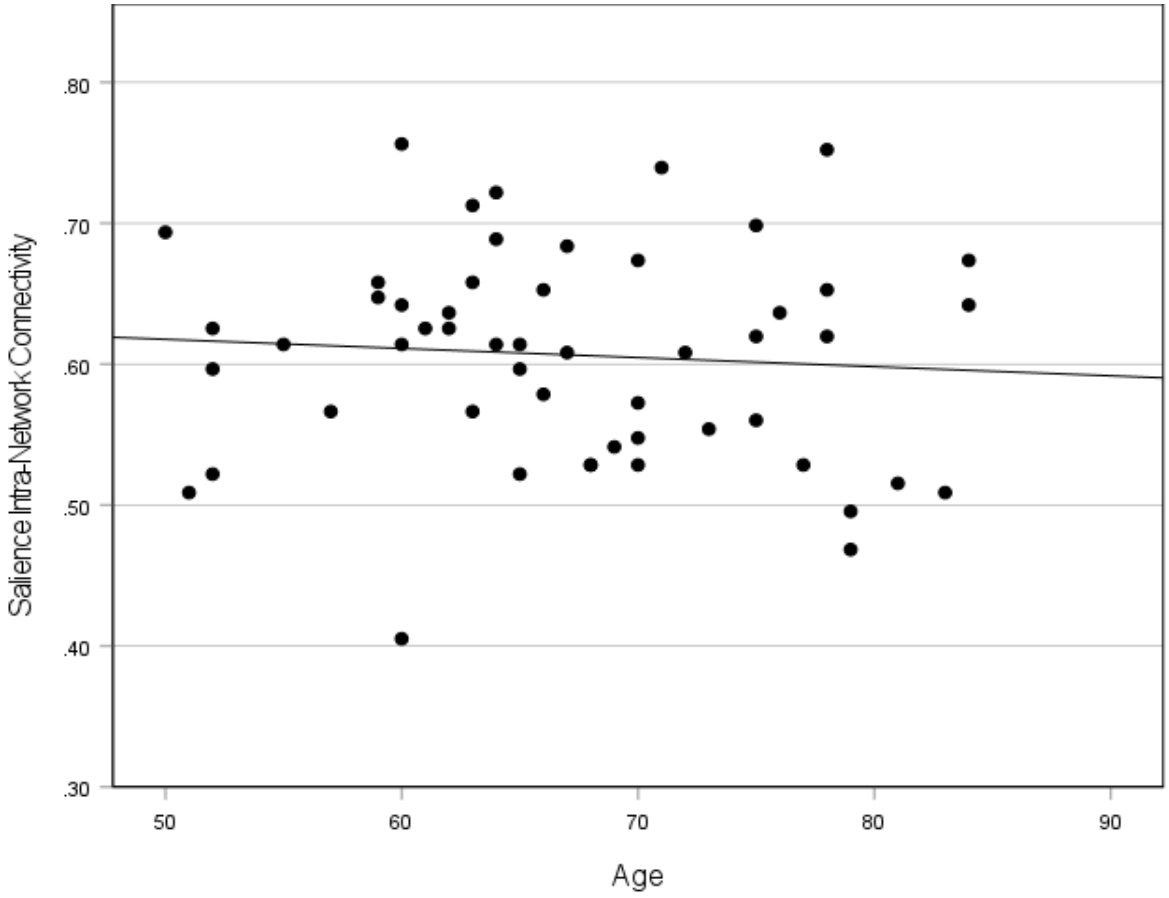


Figure 6: Relationship between age and average inter-network connectivity between the default mode, salience, and fronto-parietal networks, represented in unstandardized correlation coefficients.

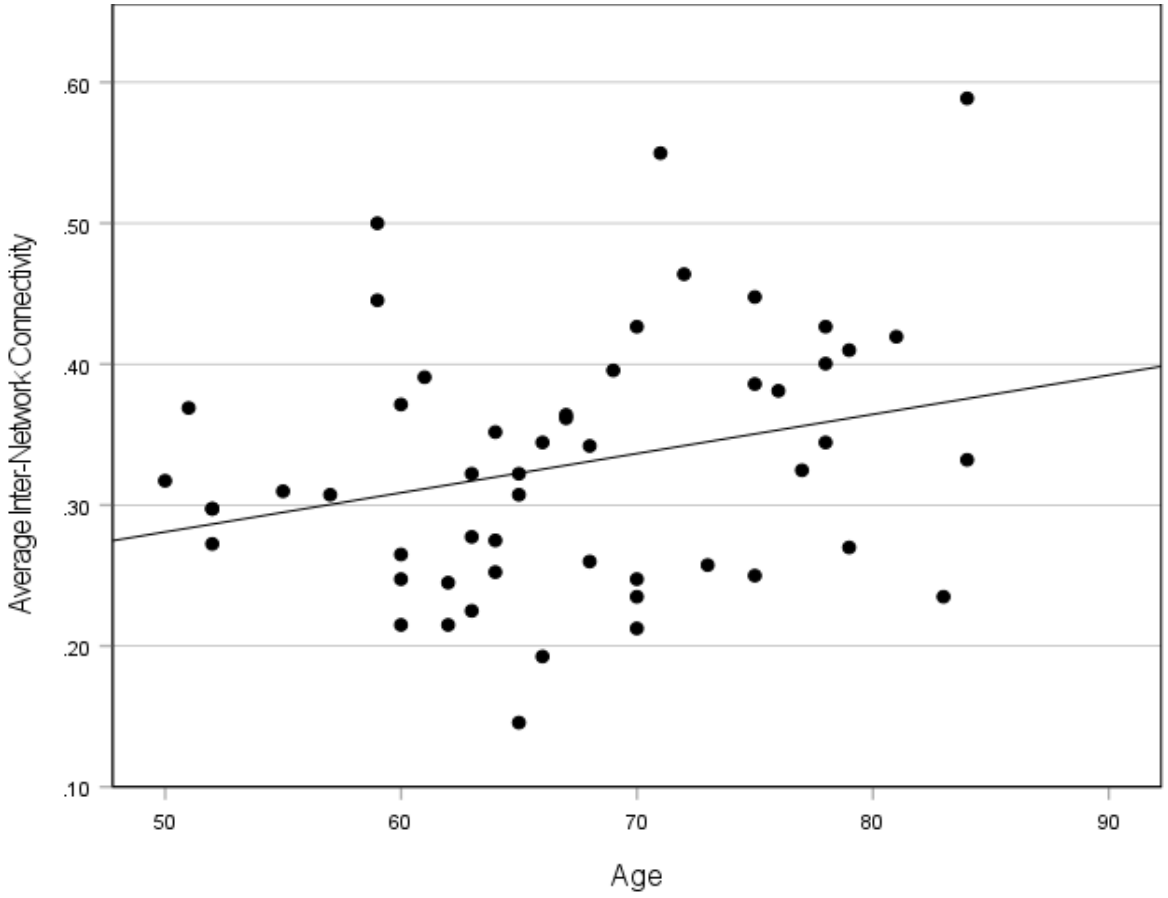


Figure 7: Relationship between intra-network connectivity in the default mode network and task performance among the active and sham groups, represented in unstandardized correlation coefficients.

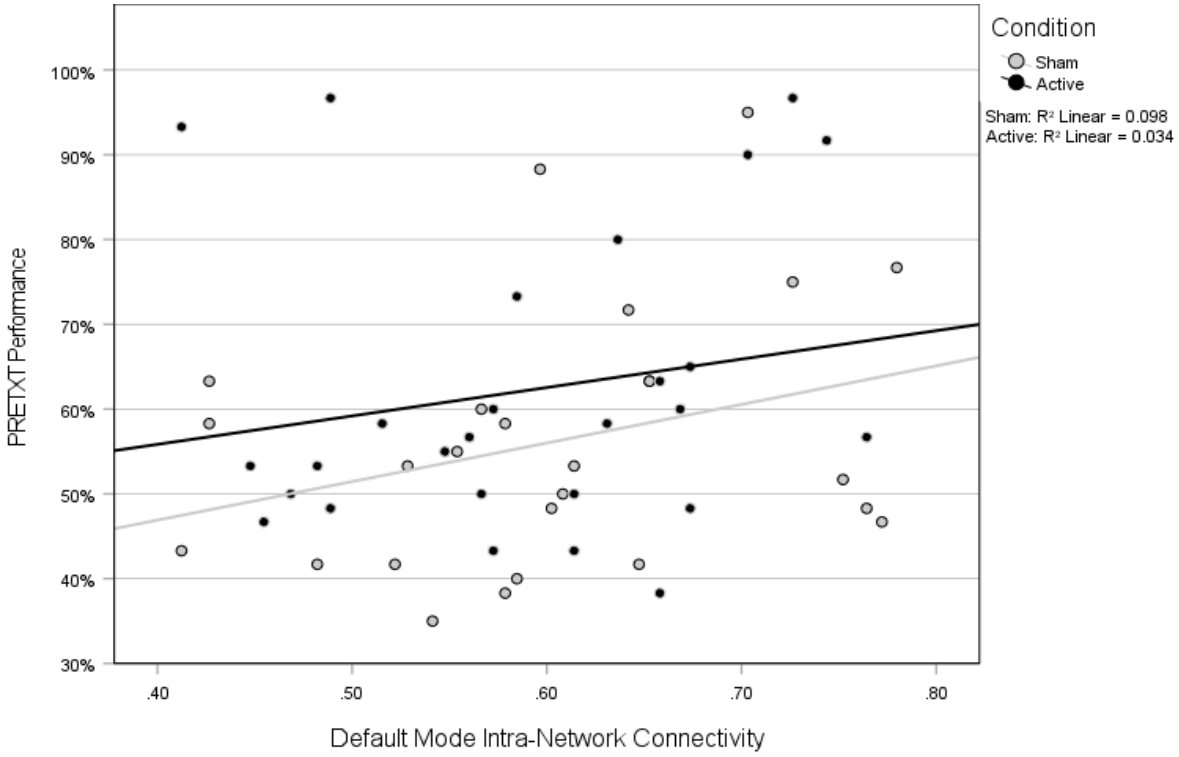


Figure 8: Relationship between intra-network connectivity in the salience network and task performance among the active and sham groups, represented in unstandardized correlation coefficients.

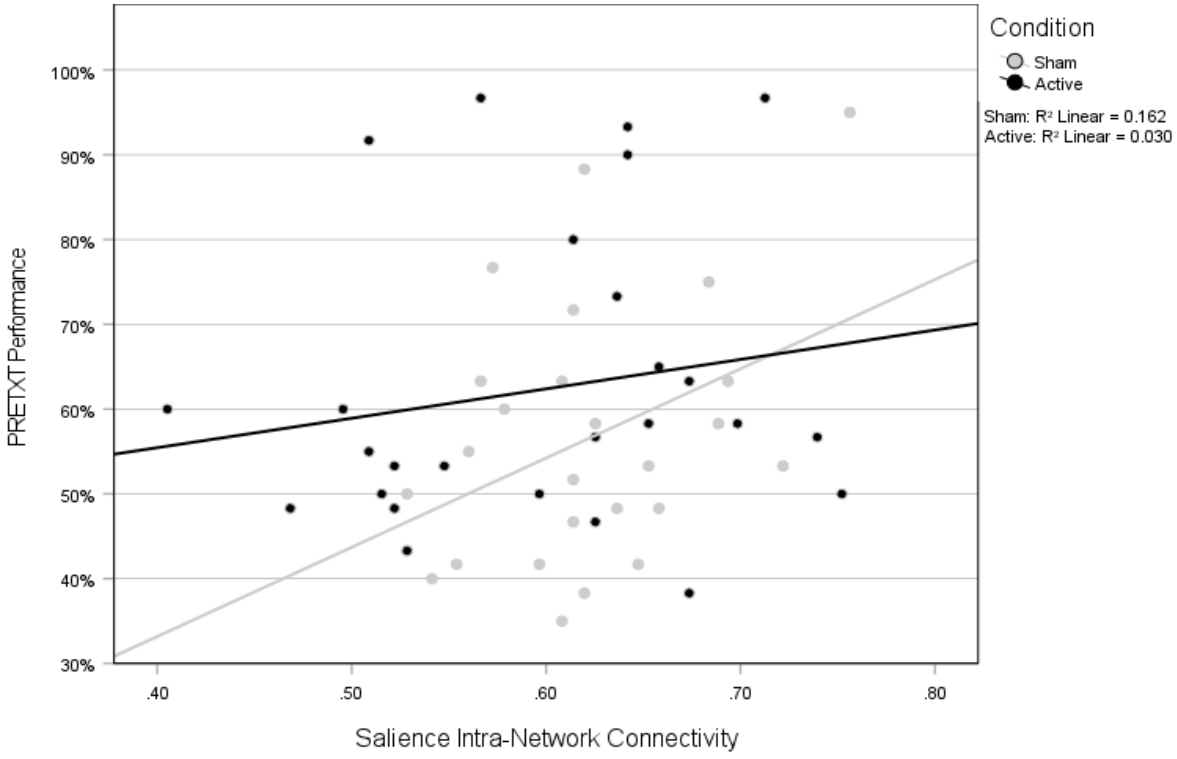


Figure 9: Relationship between intra-network connectivity in the fronto-parietal network and task performance among the active and sham groups, represented in unstandardized correlation coefficients.

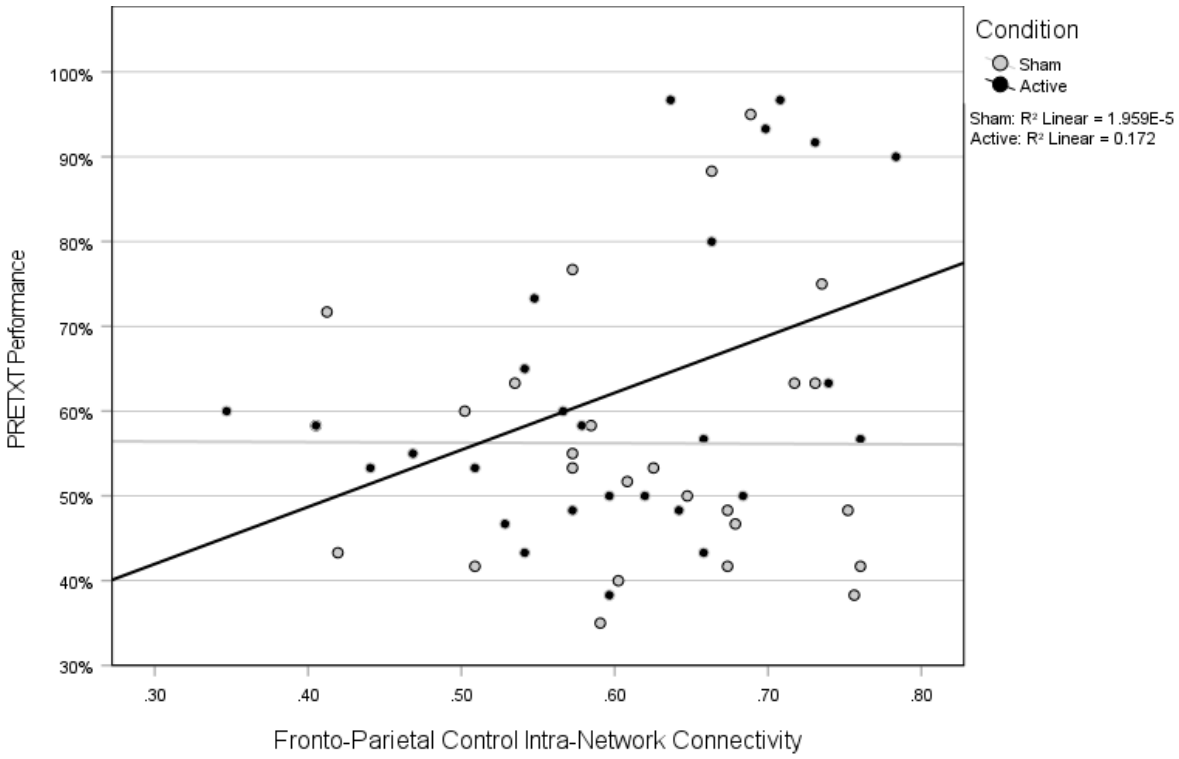


Figure 10: Relationship between average inter-network connectivity between the default mode, salience, and fronto-parietal networks and task performance, represented in unstandardized correlation coefficients.

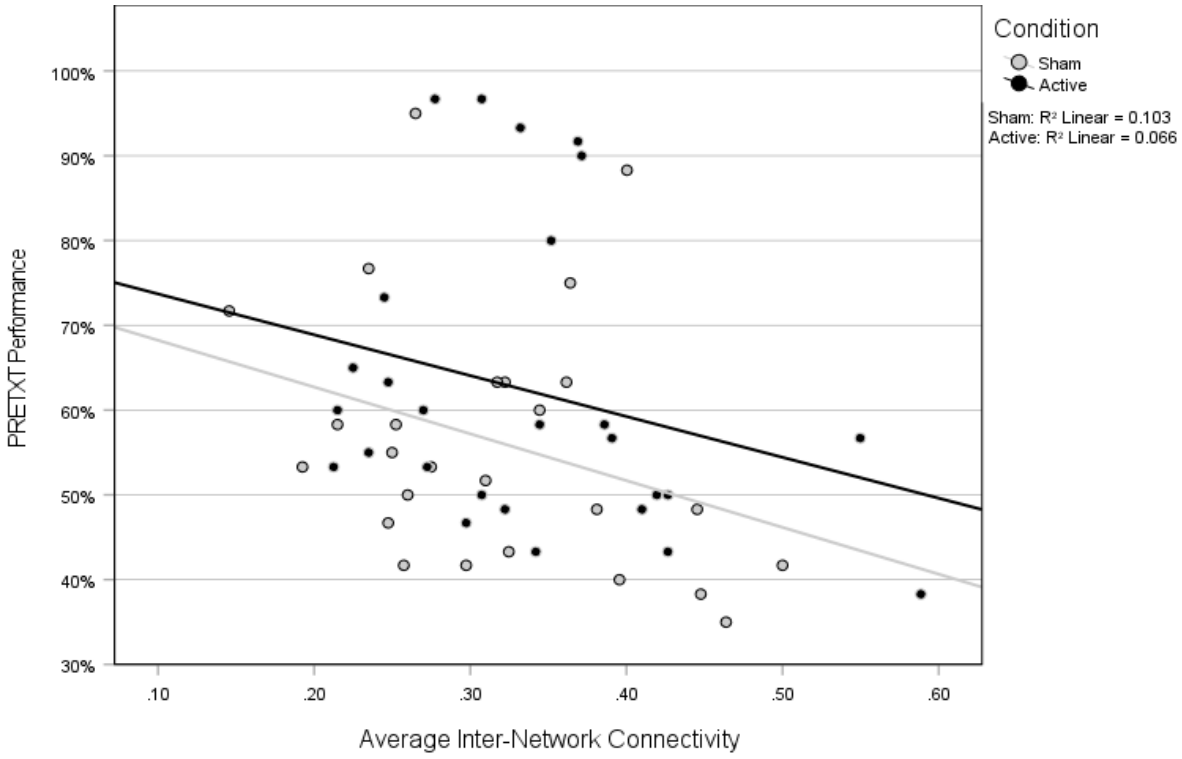
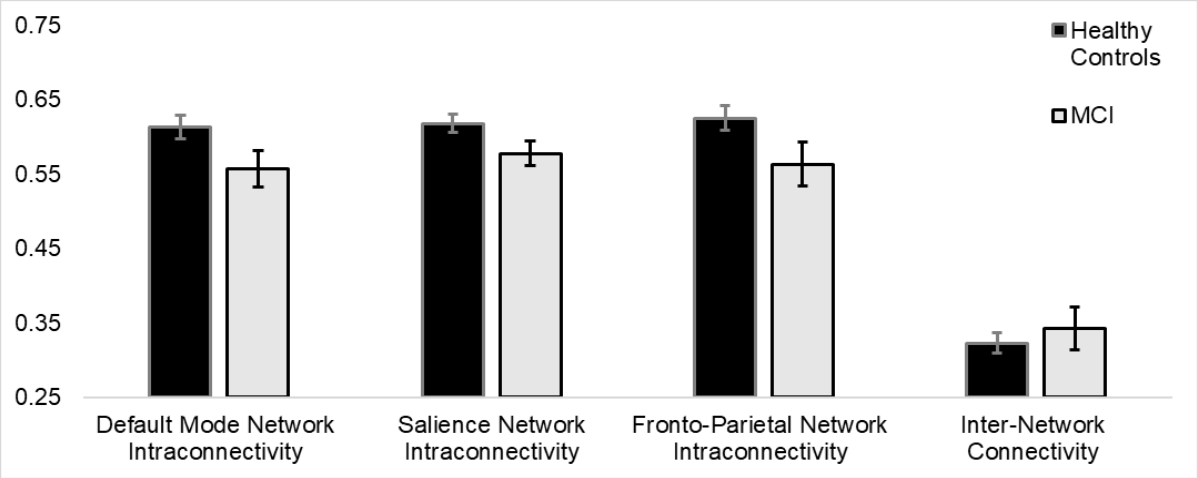


Figure 11: Differences in average inter-network connectivity between the default mode, salience, and fronto-parietal networks and task performance and intra-connectivity within each of these networks in the healthy control and MCI groups. Y-axis represents represented in unstandardized correlation coefficients. Error bars +/- 1 SE.



Tables

Table 1: *Sample Demographics*

	Total (N=53)	Active (n=27)
	Mean (SD) or n (%)	Mean (SD) or n (%)
Age	67.1 (8.9)	67.9 (10.3)
MCI	15 (28.3)	8 (29.6)
Male	23 (45.2%)	12 (44.4%)
Black	2 (3.7%)	0 (0%)
Hispanic	11 (20.7%)	4 (14.8%)
Native American	2 (3.7%)	1 (3.7%)
White	38 (71.7%)	23 (81.4%)

Table 2: *Age predicting intraconnectivity in the DM, FP, and salience networks and average interconnectivity*

	Variable	B (SE)	β	t	p	R^2
Model 1	DM Intraconnectivity	-0.003 (.003)	-0.17	-1.25	0.217	0.17
Model 2	FP Intraconnectivity	-0.005 (0.003)	-0.25	-1.82	0.074	0.25
Model 3	Salience Intraconnectivity	-0.001 (0.002)	-0.07	-0.5	0.616	0.07
Model 4	Average Interconnectivity	0.004 (<.002)	-0.27	2.04	0.046	0.28

Table 3: *Intraconnectivity in the DM, FP, and salience networks and average interconnectivity predicting PRETXT performance in the active group*

	Predictor	B (SE)	β	t	p	R^2
Model 1	DM Intraconnectivity	22.11 (20.41)	0.21	-1.08	0.289	0.21
Model 2	FP Intraconnectivity	41.53 (16.72)	0.44	2.48	0.02	0.44
Model 3	Salience Intraconnectivity	19.09 (22.59)	0.17	0.84	0.406	0.17
Model 4	Average Interconnectivity	-35.23 (25.83)	-0.26	-1.36	0.185	0.26

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