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Evaluating an Approach to Improving Attention Networks by Theta Stimulation

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Abstract

There has been wide interest in the role of neuromodulation in improving cognitive performance of persons who have suffered deficits due to disorders or in persons seeking to improve baseline performance. We summarize human and animal experiments suggesting that exogenous electrical stimulation of targeted areas of the human brain together with a task activating the same area might improve connectivity by increasing Fractional Anisotropy (FA). In this study we recruited 14 normal undergraduate volunteers who underwent 20 days of theta electrical stimulation from scalp electrodes while performing the Attention Network Test. We found evidence of improved overall reaction time over the first three days of practice, enhanced ability to resolve conflict over the first 15 days, and increased intrinsic theta near the anterior cingulate cortex (ACC). While, we did not find evidence of enhanced FA either in pathways surrounding the ACC close to the targeted area, nor in control pathways far from the target of stimulation, the data suggest this line of research warrants further study.

Introduction

In this paper we consider the hypothesis, based on our human and mouse studies, that white matter connectivity can be altered by appropriate stimulation at the theta frequency [1,2]. In one study we used optogenetics to change the output of cells in the mouse anterior cingulate cortex (ACC) at 1, 8 or 40Hz. The g ratio (diameter of axon/ axon diameter + myelin) was significantly reduced in brain areas near the ACC, but not in areas far from stimulation [2]. The improved connectivity correlated with behaviors indicating reduced anxiety [3].

In another study, we tested whether we could improve intrinsic theta in the human brain. We compared the effects of 6Hz theta stimulation via scalp electrodes, auditory stimulation, and biofeedback [4]. Each method was carried out in a single, one-hour long session and was performed either alone or during performance of the Attention Network Test (ANT), which is known to activate the ACC [5]. The largest increase in intrinsic theta in the ACC was found when targeting the ACC with 6 Hz stimulation while the participant performed the ANT [4]. The study also showed a greater theta amplitude increase in the ACC following targeting that structure than when targeting a control area, the primary motor cortex (PMC). When targeting the PMC, intrinsic theta was enhanced more in the PMC than in the ACC., These results confirm some specificity of target location when stimulating by scalp electrodes.

Based on these findings, we hypothesized that exogenous stimulation through scalp electrodes while practicing the ANT over many days might produce detectable changes in white matter, reflected in larger fractional anisotropy (FA) in a study using Diffusion Tenor Imaging (DTI). We also expected to find improvement in conflict processing, perhaps supported by the structural change in connectivity.

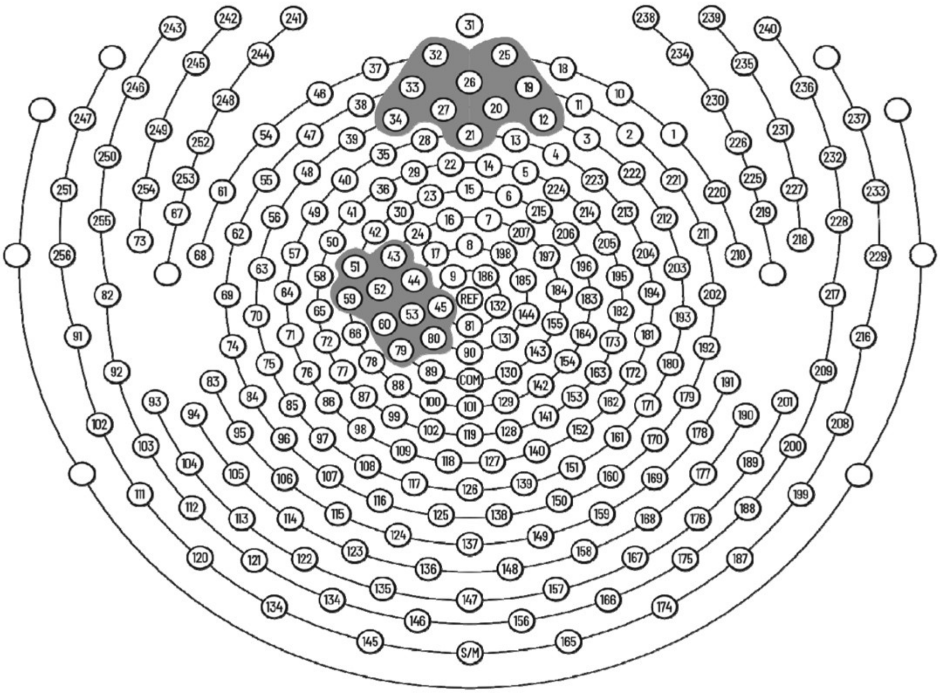

Figure 1: 256 electrode array, the dark midline frontal area at the top of the figure indicates the ten electrodes used to target the ACC, while the lower dark area on the left side indicates electrodes used to target the PMC. Electrode array figure from [4].

Twenty Day Study

Methods

Experimental design: Based on our previous findings [4], we gave fourteen undergraduates 20 days of electrical stimulation from a 256 electrode geodesic sensor-net. The generic electrodes appropriate for targeting the ACC are located over the frontal midline as shown in Figure 1. Generic configurations of electrodes were used for measurement of theta activity in the underlying brain region while individual configurations were developed for optimal targeting of the individual participant's ACC. Stimulation of the ACC was carried out while the person performed the ANT.

We first selected individual electrodes for the stimulation of each participant based on the first structural scan, taken one month prior to stimulation [6]. This configuration was used throughout the stimulation series. After each scan, we registered the DTI to a structural image of the same brain.

We used DTI to assay changes in the six white matter pathways that were improved in our earlier meditation study as well as two control pathways remote from stimulation [7,8]. Our main hypothesis was related to FA immediately before and immediately after the stimulation. We also collected structural MRI and DTI one month before stimulation and after ten days of the experiment in order to identify changes specific to the training period.

Each day of stimulation consisted of an initial 2-minute baseline EEG while the participant sat quietly with eyes open. They performed the ANT while receiving one minute of stimulation at 6 Hz through 10 pairs of electrodes, totaling 1 mA of current (see Figure 1). This was followed by one minute of no stimulation while continuing to perform the task and the cycle repeated two more times to complete a 6-minute block. Two more 6-minute blocks were then performed, followed by another 2-minute baseline measurement, for a total of about 30 minutes of EEG measurement per day.

Analysis: The EEG data were processed to look for changes in theta amplitude across days, twenty samples of 30-second periods were selected and averaged for each category (beginning baseline, tACS+ANT, and ending baseline) as described previously [4]. Of the 20 training days, some comparisons were made by averaging ANT results and theta levels for the first three (1,2,3), the middle three (9,10,11), and last three (18,19, 20) days and performing *t*-tests for between-block differences and repeated measures analysis for changes over time.

The DTI data were processed using region-specific masks to generate a FA summary statistic for each region. To compare across participants, we first registered the FA data to the T1 anatomical images with a linear transformation using FMRIS software library's (FSL) Linear Image Registration Tool (FLIRT) [9]. We then registered anatomical images to MNI space with a nonlinear transformation (FLIRT + FNIRT). The data were processed to correct for distortions using the FSL tools eddy [10] and topup [11] and DTI values were calculated using dtifit (https://fsl.fmrib.ox.ac.uk).

There were six regions of interest close to stimulation: the left and right anterior and superior corona radiata and the body and genu of the corpus collosum. The control regions were posterior and far from the target of stimulation: the splenium of the corpus callosum and posterior thalamic radiation. A mean was taken separately of the experimental and control measurements; these were then compared using a t-test to look at group differences between MRI sessions 2 and 4 (directly before and after theta training).

Results

As shown in Figure 2, top panel, there was improvement in overall ANT reaction time (RT) only over the first few days of practice. Across days 1-3 there was a significant reduction in RT ($F(2,26) = 6.90$, $p = 0.004$). Following day 3 there was no further significant decline. There was more prolonged improvement in the time to resolve conflict (Figure 2, bottom panel). We compared the first three, middle three and last three days and found a significant decline in conflict scores ($F(2,26) = 33.83$, $p<0.001$). These differences may have been purely due to practice in the task, but usually overall RT and conflict scores are highly correlated. We speculate that the overall RT reflects

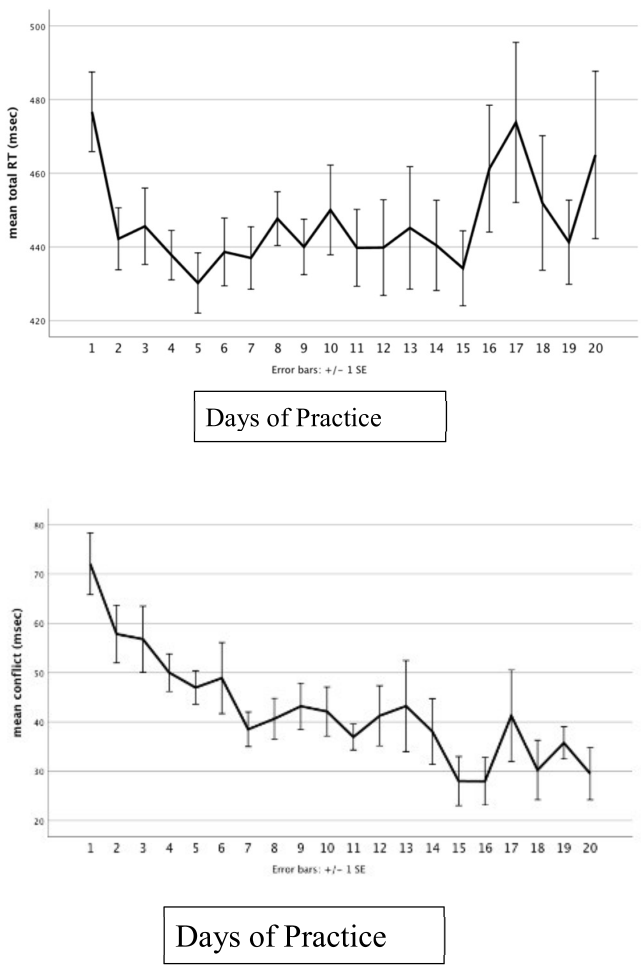

Figure 2: Mean overall reaction times (top panel) and conflict scores (bottom panel) for each of the twenty days of the experiment.

motivation of the students, while the conflict score is related to changes in the ability to resolve conflict.

Table 1 shows the amount of intrinsic theta at baseline and following stimulation during the early, middle and late days. For each of the three groups the initial baseline amount of theta is significantly less than the amount following stimulation [beginning days $t(13) = 7.44$, $p<0.001$; middle days $t(13) = 6.99$, $p<0.001$; ending days $t(13) = 5.32$, $p<0.001$). This reflects an increase in theta amplitude immediately following stimulation. The longer term effects of theta stimulation are reflected in changes in baseline between beginning, middle and ending days. The initial baseline improved significantly over days [comparing the early, middle, and late days ($F(2,26) = 3.72$, $p = 0.039$)]. The ending baseline also improved significantly over the same days [$F(2,26) = 4.89$, $p = 0.016$], but the end baseline also involved short-term effects. Thus, the targeted stimulation plus task did seem to result in increased intrinsic theta between day interval as well as within days. Since there was no unstimulated control condition this effect could have been due to practice or another non-specific effect.

Table 2 shows the mean FA values for the six experimental pathways near the site of stimulation and the two control pathways remote from stimulation immediately before stimulation (MRI session 2) and immediately after the last stimulation (MRI session 4). There was no evidence for improvement in white matter in either experimental or control pathways comparing each immediately before (session 2) and immediately after the twenty days of theta stimulation (session 4) [experimental group $t(13) = -0.62$, $p = 0.54$; control group $t(13) = -0.55$, $p = 0.59$]. The difference in overall FA between control and experimental pathways may reflect the larger overall size of the control pathways. We also collected DTI one month before stimulation (session 1), and after ten days of stimulation (session 3). The only significant difference in FA values was that the control pathways showed higher FA at session 1 in comparison with each of the later MRI sessions ($F(3,39 = 2.88$, $p = 0.048$). The same direction of larger FA at session 1 was found in the experimental pathways but this was not significant ($F(3,39 = 1.45$, $p = 0.24$). For the pathways close to stimulation there is clearly no evidence of a change in FA as a result of stimulation.

Discussion

Our main hypothesis was that stimulation plus task would enhance connectivity in pathways surrounding the ACC by increasing FA. Table 2 clearly shows that FA did not increase between MRI sessions 2 and 4 in either experimental or control pathways. We did find improved resolution of conflict and intrinsic theta after stimulation in comparison with before stimulation, but we cannot be sure that this was caused by the stimulation.

We do not know why there was no white matter change. One possibility is that this is a consequence of the fact that DTI at MRI session 1, one month before the first day of theta stimulation, was somewhat higher than session 2 immediately before stimulation. We don't know why this occurred, but it was significant only in the control and not the experimental pathways. From sessions 2 to 4, FA seemed remarkably stable in all pathways. Perhaps the elevation at session 1 could be due to increased movement or anxiety associated with initial exposure to the scanner. If this general reduction continued over the next two sessions, it could have overridden any improvement in FA we measured. However, the lack of evidence of change in the control pathways between sessions 2 and 4 argues against this idea.

Although intrinsic theta did increase over days, perhaps this was not sufficient to activate dormant oligodendrocytes which we believe is essential for changes in FA due to myelination. Although individual configurations were used in the electrical stimulation, targeting the ACC did not preclude some current influencing a more widespread

Mean value	Mean beginning baseline theta	Stimulation theta	Change in theta (stimulation - beginning baseline)
Days 1,2,3	1.07 (0.063)	1.46 (0.070)	0.40 (0.054)
Days 9,10,11	1.17 (0.060)	1.48 (0.067)	0.31 (0.044)
Days 18,19,20	1.13 (0.055)	1.44 (0.063)	0.30 (0.057)

Table 1: Mean amount of intrinsic theta and (Std Error) at baseline early, middle and late days.

Mean (SE)	S1 (pre)	S2 (before)	S3 (mid)	S4 (post)
Experimental	0.487 (0.0060)	0.485 (0.0065)	0.482 (0.0063)	0.484 (0.0061)
Control	0.549 (0.0079)	0.544 (0.0075)	0.545 (0.0081)	0.545 (0.0073)

Table 2: Mean and (Std Error) for FA values for the six experimental and the two control pathways at MRI sessions S1-4. N=14.

effect across brain regions. This stimulation method was less specific than in our mouse study [3,4] and this might have reduced the effectiveness of the treatment. Another possibility is that the electrical stimulation affected a specific sub-region of the ACC and that averaging FA across larger portions of the ACC white matter made it more difficult to detect an effect. A more tailored investigation of ACC white matter integrity and its connectivity to other specific systems could help delineate some of these possibilities but would come with greater technical challenges and computational expense.

Some studies of short-term theta stimulation either by scalp electrodes or by auditory stimulation have found improvements in attention [12] and memory [13,14]. These studies use stimulation far too short to be likely to improve white matter. However, they may have changed synaptic plasticity since it has been shown that synchronizing stimulation designed to produce long-term potentiation with theta can enhance plasticity [15].

One study directly compared theta and alpha band stimulation over the frontal midline [16] at the same time participants performed a conflict-related task. They found that the theta band stimulation reduced conflict more than did alpha stimulation. Another study compared Transcortical Magnetic Stimulation (TMS) in the theta band with standard repetitive high frequency TMS and sham controls [17]. Both TMS protocols improved performance in some individual tasks but the theta stimulation resulted in superior performance in memory and cognitive control tasks overall.

In our twenty-day experiment there was some evidence that the stimulation may have had an effect on the ability to resolve conflict. Because of our design we cannot argue for a causal effect of stimulation on conflict resolution. However, we correlated FA levels following all stimulation (MRI session 4) with the size of the conflict score just preceding it (the average of days 18-20) and did find a significant relationship between the two for one of the experimental tracts (genu of the corpus callosum) [$r(14) = -0.54$, $p = 0.045$]. Time to resolve conflict decreased with increased FA of the genu. Conflict levels averaged from days 1-3 were not correlated with FA of the genu at session 2 (taken just before) [$r(14) = -0.25$, $p = 0.389$], but conflict averaged during days 9-11 approached a significant correlation with FA of the genu (taken between days 10 and 11) [$r(14) = -0.52$, $p = 0.060$]. Thus, it is possible that there is a relationship between improved connectivity of the genu and increased efficiency of conflict resolution, but the design and limited number of subjects requires more research.

Although our effort to alter white matter in the human brain through stimulation from scalp electrodes was not successful it may still warrant further research. There is some evidence that deficits present in substance abuse may be successfully treated by mindfulness meditation [18,19] which has also been shown to increase intrinsic theta [20]. In one study using mindfulness training in comparison with relaxation training a decrease in tobacco use was related to increased connectivity between the ACC and striatum [18]. While theta was not measured in this study similar meditation training has resulted in increased frontal theta [20]. In another study using mindfulness training the best predictor of reduced use of opioids was an increase of frontal theta [19]. These studies and the possible improvement in attention and memory with short-term stimulation both support the need for more research in this area.

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