The Darrell K Royal Research Fund for Alzheimer's disease
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Austin, TX 78763
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Friday, April 20th, 2018

Dear Mrs. Edith Royal, the DKR Fund Board of Directors, and Scientific Research Committee:

It gives me great pleasure to submit this annual report for the scientific research project titled "Non-invasive brain stimulation to improve memory retrieval in patients with mild cognitive impairment".

Mild Cognitive Impairment (MCI) commonly represents the 'at-risk' state of developing AD with the major subtype 'amnestic MCI' (aMCI) typically presenting disturbances in memory retrieval. Given that the neurodegeneration in AD may be too severe to be treated, research studies focus on prodromal stages of AD, such as Mild Cognitive Impairment (MCI). The limited effectiveness of pharmacological treatments for cognitive impairment in amnestic MCI/AD has led to an increased interest in research on alternative treatment options.

Our team has extensive experience with non-invasive brain stimulation as a treatment for neurological and psychiatric disorders and has recently piloted the technique of High Definition-transcranial Direct Current Stimulation (HD-tDCS). We propose HD-tDCS as an alternative treatment to improve word retrieval in patients with MCI. With support of this grant, this project will lead to more insight into the mechanism underlying word retrieval in MCI patients and can lead to significant progress in developing a novel effective treatment for cognitive dysfunction in MCI patients leading to Alzheimer's disease.

With support of this grant, this project help us to get more insight into the mechanism underlying word retrieval in MCI patients that could potentially lead to significant progress in developing a novel effective treatment for cognitive dysfunction in MCI patients leading to Alzheimer's disease.

With the warmest regards,

Sven Vanneste, Ph.D.

We finalized two projects that fall under the umbrella of this grant. In a first project, we looked at the role of posteromedial cortex (PMC)—comprising posterior cingulate cortex (PCC), retrosplenial cortex (RSC), and the precuneus— that is best known for its involvement in the default mode network. There is no consensus regarding the specific function of PMC, however, and its subregions each exhibit distinct but partially overlapping functional profiles. To date, there has been no large-scale effort to disentangle the functions of these regions. In the first study, we used Neurosynth (http://neurosynth.org) to conduct an unbiased meta-analysis of the PCC/Precuneus area based on fMRI coactivation and semantic information extracted from 11,406 studies. Our analyses revealed six PMC clusters with distinct functional profiles: superior and inferior dorsal PCC, anterior and posterior precuneus, ventral PCC, and RSC (see figure 1 & 2). We discuss these findings in the context of the existing literature and suggest several fruitful avenues for continued research. This first project is submitted for publication to a scientific journal.

In a second project, we hypothesized that the involvement of PCC, particularly its gamma band activity, is critical for successful memory retrieval. To test this, we designed two experiments to examine whether HD-tDCS can enhance gamma band activity in PCC as well as subjects' performance in a language memory test. We demonstrated HD-tDCS can significantly enhance gamma band activity of PCC in active stimulation group compared to sham stimulation group. Furthermore, we also revealed that participants who received active stimulation would perform better in the language retrieval test than participants who received sham stimulation. This second project is finalized and will be submitted for publication to a scientific journal.

For our third project the goal was to entrain the retrieval network using HD-tDCS targeting the PCC in order to improve word retrieval in impaired MCI patients using behavioral and electrophysiological markers to assess outcomes. In the first year of funding, the focus was placed on getting all formalities completed and participant recruitment. Since the study involves human subjects recruited from the University of Texas Southwestern Medical Center (UTSW) Alzheimer's Disease Center (ADC) (funded by the national Institutes of Health's National Institute on Aging, of which Dr. John Hart, the co-PI of the study, is the co-Clinical Core Director), approval from the UTSW and UT Dallas Institutional Review Boards was required. This study is approved by both UTSW and UT Dallas. Recruitment of patients with Mild Cognitive Impairment through our established referral network is operational. However, many MCI patients at the University of Texas Southwestern Medical Center (UTSW) Alzheimer's Disease Center (ADC) were already enrolled in other research studies in the past year, making it impossible to refer them in for our study. To address this issue, we have coordinated with other research teams at University of Texas Southwestern Medical Center (UTSW) Alzheimer's Disease Center (ADC) to refer participants to our study when they are either ineligible for their study or when they finished the procedures for their study. After screening and enrollment, we started administering 6 sessions of 20 minute of 1 mA HD-tDCS targeting the PCC region in patients with mild cognitive impairment (Aim 1). All subjects enrolled in the study were assessed for behavioral performance, neuropsychological, and EEG/ERP measures of word retrieval (Aim 2). We collected the data and are now analyzing these. Preliminary analysis show promising effect indicating that HD-tDCS can indeed selectively improve word retrieval in patients with MCI (see figure 3). At the conclusion of this study, the development of HD-tDCS as a noninvasive, non-pharmacological treatment for cognitive dysfunction in MCI patients will provide a novel, targeted therapeutic intervention with limited side effects or drug interactions that could potentially be added to other medical treatment regimens.

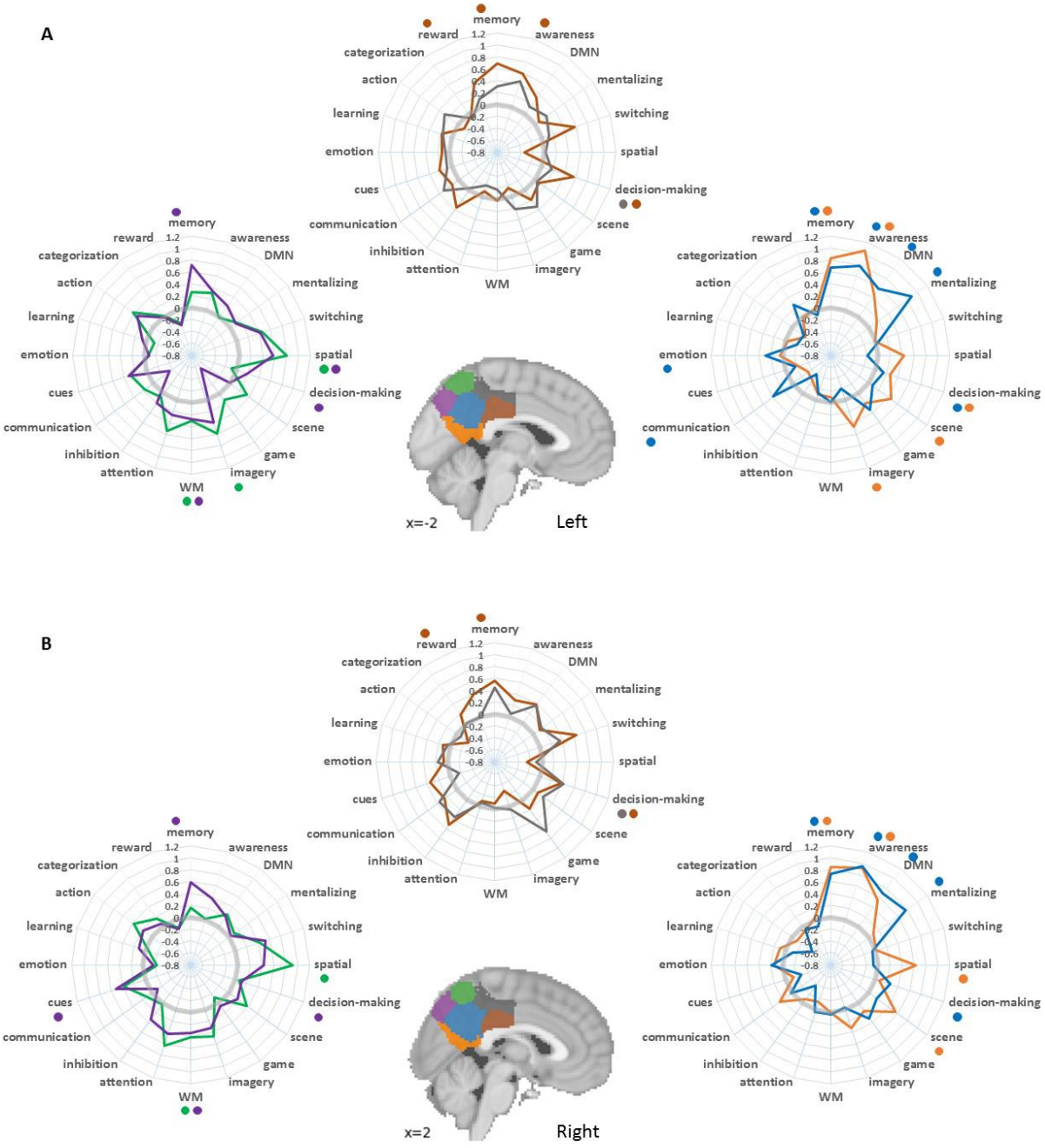

Figure 1. Result for the functional lateralization analysis on cognitive related functions. **A**. Sagittal view of left PMC mask (x = -2) and radar plot of the 20 functions' preference profiles for all 6 clusters in left PMC. **B**. Sagittal view of right PMC mask (x = 2) and radar plot of the 20 functions' preference profiles for all 6 clusters in right PMC. Strength of preference profiles is measured in LOR, and permutation-based significance are $p < 0.01$ (FDR), which indicated by color-coded dots corresponding to each region.

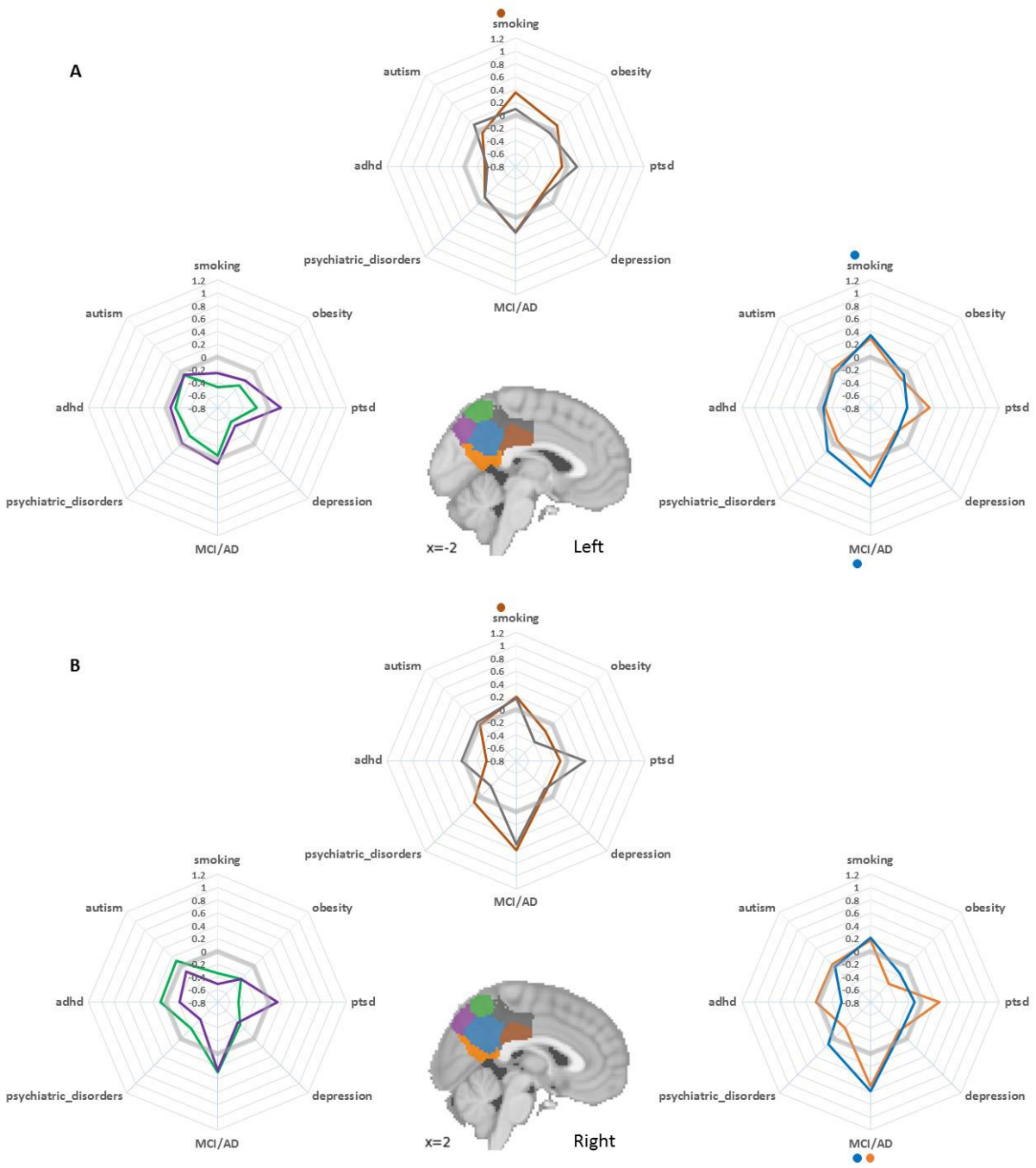

Figure 2. Result for the functional lateralization analysis on disorder related functions. **A**. Sagittal view of left PMC mask (x = -2) and radar plot of the 8 disorders' preference profiles for all 6 clusters in left PMC. **B**. Sagittal view of right PMC mask (x = 2) and radar plot of the 8 disorders' preference profiles for all 6 clusters in right PMC. Strength of preference profiles is measured in LOR, and permutation-based significance are $p < 0.05$ (FDR), which indicated by color-coded dots corresponding to each region.

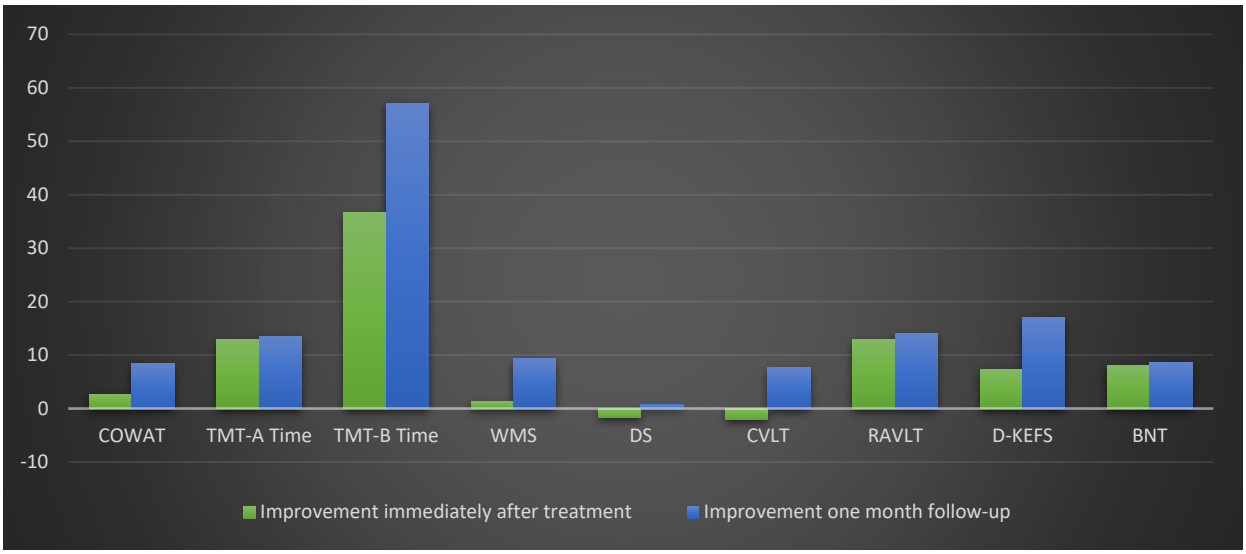

Figure 3. Changes on the difference clinical measures. (Positive numbers show improvement; Negative numbers show a worsening).