Towards Development of a Circuit Based Treatment for Impaired Memory: A Multidisciplinary Approach

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Abstract— **The previous decade saw progress in our understanding of fundamental neural systems of the brain, particularly those sub-serving memory. For example, it is now recognized that individual power and peak frequency attributes of alpha band rhythms predict performance on a working memory task. Additionally, investigators using transcranial magnetic stimulation (TMS), a safe and non-invasive means of stimulating the awake and alert human brain, have shown TMS can mimic long-term potentiation (LTP), widely considered the neurophysiologic substrate of memory. Based on this earlier work, we designed a combined TMS-EEG study of the effects of 10Hz rTMS on psychomotor processing speed, an index of neural efficiency, on a well validated short-term verbal recognition memory task, the Sternberg. We predicted first, that compared with sham 10Hz repetitive transcranial magnetic stimulation (rTMS) would significantly reduce psychomotor processing speed indexed as reaction time (RT). Second, we predicted that improvement in RT would be associated with a 10Hz rTMS induced increase in pre-task alpha power and pre-task alpha band phase synchrony.**

I. Introduction

Schizophrenia has been recognized for more than a century as a psychotic disorder in which psycho-social recovery is uncommon, principally due not to psychotic symptoms which are relatively easy to treat, but to disabling impairment of cognitive functions first recognized by Emil Kraepelin in 1893 [10]. Kraepelin described poor outcomes in social functioning, associated with impairments of attention, motivation, problem solving, learning, and memory as the principle features of this disorder. Kreapelin's assessment still holds — less than 15% of patients with schizophrenia recover [2], [11]. There is still no treatment for cognitive dysfunction seen in schizophrenia or other neuropsychiatric disorders [7], [12], [14]. Recent reports from the NIMH supported MATRICS researchers regarding the development of a consensus for a standardized battery of neuropsychological instruments to identify and measure the principal cognitive deficits of schizophrenia reinforces the importance of cognitive impairment in schizophrenia [6]. With regard to our study, it is also notable that psychomotor processing speed measured as reaction time received a strong endorsement for inclusion in the MATRICS test battery.

A. Multiscale origins of cognitive function and impairment

On the molecular scale, emerging evidence supports a model of cognitive impairment in schizophrenia that is associated with a complex array of polymorphic alleles. Such variants have been shown to be associated with inheritable impairments of cognitive function [3], [13], [16]. So far, attempts to develop new pharmacologic agents based on these important genetic findings have not been successful. In this regard, our plan to develop a macro-scalar (neural circuit) approach to impaired memory using alpha frequency (10Hz) rTMS is supported by evidence showing a predictive relationship between EEG alpha band power and working memory task performance [1], [4], [8], [15]. Evidence to support the relationship between cognitive deficits in patients with schizophrenia and low alpha spectrum power in the Dorso Lateral Pre-Frontal Cortex (DLPFC) of first episode, neuroleptic naïve patients with schizophrenia is also supported by the study of Ford and colleagues [5] who found reduced fronto-temporal alpha band coherence in an auditory event related potential study comparing healthy subjects with patients. Finally, the study of Klimesch [9] lends strong support for this work. These investigators compared alpha frequency rTMS, sham and 20Hz rTMS, directed to the frontal, parietal or occipital cortices. Important to our goal of developing a circuit based treatment model for impaired memory, studies show that compared to healthy subjects patients with schizophrenia have lower prefrontal alpha band power and lower peak alpha frequency [5].

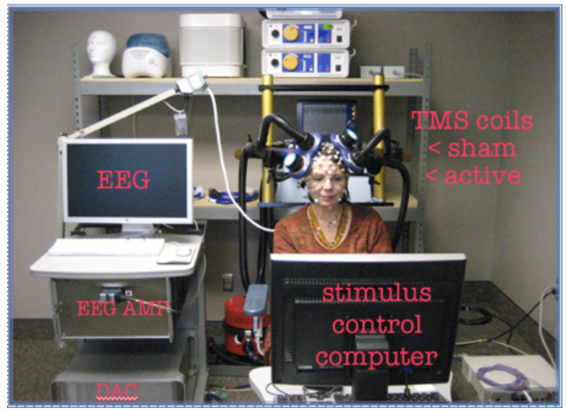

Fig. 1. Setup apparatus for rTMS application, paradigm presentation, and EEG acquisition.

II. Experimental Design

A single blind, sham controlled study of the effects of 10Hz rTMS on RT in a short-term recognition memory task. Figure 1 shows the experimental setup. Healthy, right-handed male (10), and female (10) subjects were trained to 70% or better accuracy on 20 trials of randomly presented and counterbalanced 5 or 7 item strings of consonants and vowels that appeared on a computer screen for 1.5 seconds, followed by a 1.5 second delay after which a single letter probe was presented. Subjects were asked to decide as quickly

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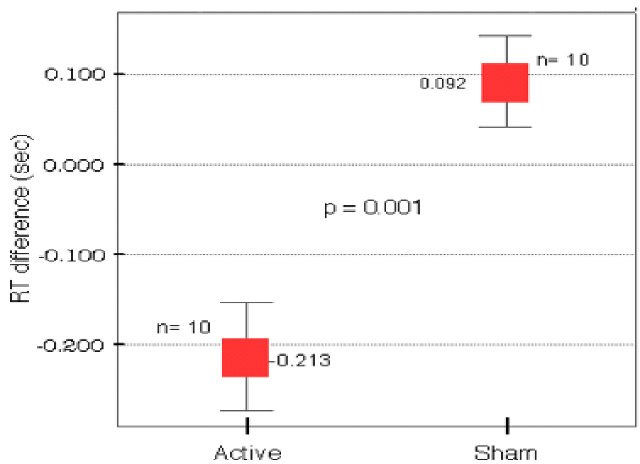

Fig. 2. Mean change in reaction time with active compared to sham 10Hz rTMS directed to the dorsolateral prefrontal cortex of healthy participants 1000ms prior to working memory task onset. The RT change is significant at p=0.001± sem. The small increase in mean reaction time for the sham treated groups is congruent with the parametric nature of the Sternberg task i.e. the post stimulation task was more difficult than the pre-stimulation training task hence, a longer reaction time is expected.

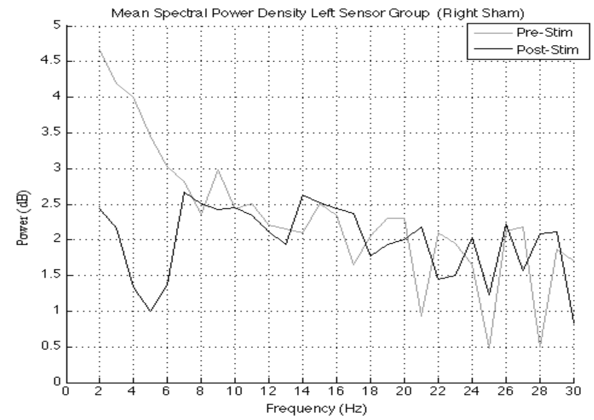

Fig. 3. Pre-frontal cortical broadband power spectral density in a subject in the sham 10Hz rTMS group exhibits no apparent change in broadband power with stimulation.

and accurately as possible whether the probe had been in the previous string by pressing a one of two keys on a keyboard. Reaction time (RT) of a response was recorded and counted if it occurred within a 5 second window after onset of the probe. Incorrect responses were not counted in the computation of RT. The mean RT of the training session was used as the baseline for subsequent comparison with post-stimulation RT. During the rTMS testing period, subjects were presented with 6 or 8 item letter strings using the same design and parameters as during the training session.

Subjects were randomly assigned to a stimulation group. The resting motor threshold (MT) was determined for all subjects in the following manner: A circular 80mm TMS coil (Fig. 1) was held in place manually at the vertex while a series of single TMS pulses were delivered at 10-second intervals. MT was defined as a visible movement in the contralateral first dorsal interosseous muscle on at least 5 of 10 trials spaced 10 seconds apart. Subsequently, the stimulator power output used to determine individual MT was the same used during the rTMS treatment phase.

A 64-channel EGI EEG high impedance system1 was used to record electrophysiological data at a 256Hz sample rate; zero gain, with an IIR 0.1Hz highpass, 100Hz lowpass digital filter. The location of the right and left scalp sensor positions overlying the probabilistic location of the DLPFC was determined according to the 10-20 international EEG measuring system. Once MT was determined a 70mm figure-eight air-cooled TMS coil (Magstim) was substituted for the 80mm round coil, with the midpoint of the coil set in contact with EEG sensors F3 and F4. This coil was held in place with the handle pointing to the rear at an 450 angle by an adjustable custom designed mechanical arm (Fig. 1). Selection of the first side to be stimulated was randomized and counter-balanced. Sham 10Hz rTMS was also delivered at MT intensity using an identical appearing air-cooled 70mm figure eight coil constructed with a non-conducting coil (Magstim Corp). Capacitor discharge in this device delivered an auditory stimulus identical to that of the active device (Fig. 1).

Participants received five 5-second trains of either active or sham 10Hz rTMS at 100% of MT, with a 12 second inter-train interval. One second (1000ms) after the last pulse train participants were presented with a series of 48 trials of a 6 or 8 item Sternberg task. This series was followed by an identical sequence of stimulation and task performance. The same sequence of events was repeated once more on the first side, and after a 10-15 minute rest, it was repeated on the opposite side for a total of 1000 pulses, and 192 Sternberg task trials.

III. Data Analysis

A. Demographic comparisons

There were no significant differences between groups for age, education, or IQ. All participants were free of any condition that would prevent their participation in a TMS study. Participants agreed to a SCID-IV research interview; no participant was found to have a diagnosable psychiatric disorder.

B. Effect of 10Hz rTMS on working memory psychomotor processing speed

Between group comparisons were computed using a one-way random effects GLM-ANOVA (SPSS 11.03). The results are displayed in Table I. The mean RT of correct responses in the training trials was used as baseline. There was no difference in baseline score (accuracy), or baseline RT between the two groups. We computed the mean score and RT of post left-sided stimulation, post-right sided stimulation, Total post-stimulation RT(Left RT + Right RT/2), and the difference between pre- and post-stimulation (Left RT - baseline RT as measure of change in RT. There was a main effect of group for each of these post-stimulation RT measures (Table I.) There was no effect of stimulation on post-stimulation scores.

C. Analysis of spectral dynamics induced by 10Hz rTMS

In order to compare the spectral effects of 10Hz rTMS, two second epochs of continuous EEG data were first extracted from the last 2 seconds of the eyes closed, pre- stimulation

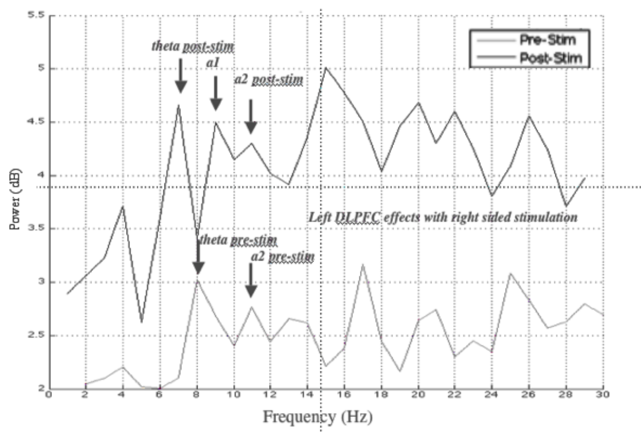

Fig. 4. Pre-frontal cortical broadband power spectral density in a subject in the active 10Hz rTMS group exhibits an apparent increase in broadband power with stimulation. 10Hz rTMS may also perturb alpha mean frequency: note the post-stimulation induction of an alpha-1 peak not present pre-stimulation.

EEG record (PreStim), and last 2 seconds of the EEG record prior to the start of the working memory task. These data epochs were pre-processed by 8-12 Hz FIR bandpass, followed by identification of artifacts greater than 100uV, and channel replacement with spherical spline interpolation (EGI Waveform tools) for channels with more than 20% of samples with greater than 100uV. Lastly, the voltage data were re-referenced to the common average. Finally, preprocessed files were exported to MATLAB 7.3 for spectral analysis.

We determined the power spectral density of the pre-and post stimulation pre-processed EEG data by first computing the power spectra of the signal extracted in the time domain. The Fast Fourier Transform was applied first to yield a phasor at each wave number. We then determined the magnitude of the phasors in order to ascertain power at a specific frequency. Phase was extracted from the directionality of the phasor. The initial phase analysis provided a phase histogram that was used to derive circular statistics. Care was taken to calculate such statistics while respecting the periodicity of the phase domain. The expression in equation (2) was used to compute phase variance; the expression in equation (3) was used to compute the phase synchrony index (PSI). Figure 5 illustrates the effect of 10 Hz rTMS on phase synchronization in a representative subject that was actively stimulated. Note the difference of post-stimulation PSI for active compared with sham 10Hz rTMS.

After the application of the above expressions to the phase histograms acquired directly from the analysis of the phasors, a metric for the synchronization of phase for the alpha frequency band is generated. Figure 5 shows the effects of 10 Hz rTMS on phase synchronization. After stimulation, the Phase Synchronization Index increases noticeably indicating that rTMS not only increases power in the alpha frequencies, but also synchronizes alpha oscillators.

Figure 4 illustrates the power spectrum of the alpha band frequencies in the same region of the DLPFC before and after 10 Hz rTMS. After stimulation, the same cortical area experienced a non-trivial increase in mean alpha power and an increase in alpha peak frequency. Increases in power and shift of the alpha peak are associated with a shorter reaction time, as reflected in Table I. Finally, our data also show an associateion between active stimulation and the degree of induced alpha band phase synchrony in the stimulated region. Sham stimulation was was not associated with perturbations of alpha power, frequency, synchrony, or improved performance.

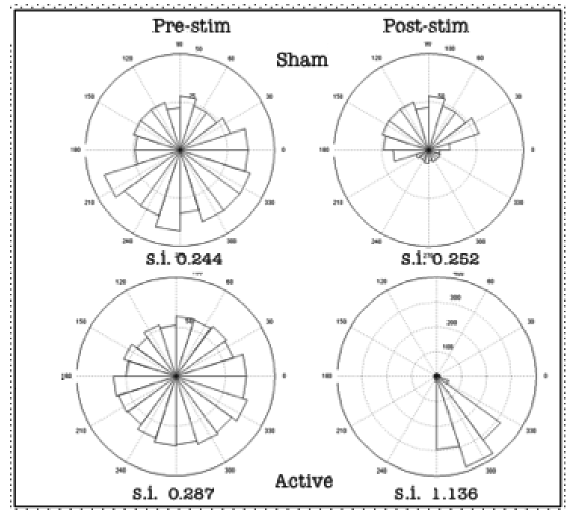

Fig. 5. Comparison of pre- and post-stimulation phase plots support the prediction that 10 Hz rTMS directed to the prefrontal cortex induces alpha frequency synchronization while sham stimulation shows no such effect.

$$\bar{\Theta} = arctan(\sum_{i=1}^{n} sin(\Theta_i), \sum_{i=1}^{n} cos(\Theta_i)) \quad (1)$$

$$Var(\Theta) = 1 - \frac{1}{n}\sqrt{(\sum_{i=1}^{n} cos(\Theta_i))^2 + (\sum_{i=1}^{n} sin(\Theta_i))^2} \quad (2)$$

$$\omega = \frac{1}{Var(\Theta)} \quad (3)$$

IV. Discussion

The prediction that compared with sham 10Hz rTMS would increase the alpha phase synchrony index was based on earlier work that found compared with periods of low spontaneous alpha phase synchronicity, periods of high spontaneous synchronicity increased the amplitude and shortened the reaction time in the auditory n100 event related potential in healthy subjects. In this light, we predicted first that compared with sham, active 10Hz rTMS would improve psychomotor processing speed indexed as RT, and second, such treatment would be associated with an increased pre-task alpha power spectral density, and a concomitent increase in alpha phase synchrony. We focused our attention on the role of the alpha band (8-12Hz) oscillatory rhythm based on earlier work [9] to show alpha power spectral density and peak frequency predicts working memory performance in healthy subjects.

Congruent with earlier work, results show that compared with sham active 10Hz rTMS directed to the DLPFC in healthy subjects 1000ms prior to performing a working memory task can improve psychomotor processing speed and can induce an increase in 8-12 Hz power and phase synchrony in healthy subjects. While earlier work demonstrated the

	δF	F	Sig
$Pre-Stim\ RT$: $BetweenGroups$	1	0.720	0.407
$WithinGroups$	18		
$Post-Stim\ RT$: $BetweenGroups$	1	5.700	0.028
$WithinGroups$	18		
$RT\ Difference$: $BetweenGroups$	1	15.262	0.001
$WithinGroups$	18		
$Left\ Post-Stim\ RT$: $BetweenGroups$	1	7.378	0.014
$WithinGroups$	18		
$Left\ RT\ Difference$: $BetweenGroups$	1	17.676	0.001
$WithinGroups$	18		
$Right\ Post-Stim\ RT$: $BetweenGroups$	1	3.981	0.061
$WithinGroups$	18		
$Right\ RT\ Difference$: $BetweenGroups$	1	11.388	0.003
$WithinGroups$	18		

TABLE I

RANDOM EFFECTS ANOVA: STERNBERG TASK REACTION TIME PRE- AND POST- 10 HZ RTMS BY GROUP

	$SumofSquares$	δF	$MeanSquare$	F	$Sig.$
$Pre-Stim\ Score$: $BetweenGroups$	0.001	1	0.001	0.084	0.775
$WithinGroups$	0.118	18	0.007		
$Total$	0.119	19			
$Post-Stim\ Score$: $BetweenGroups$	0.001	1	0.000	0.044	0.836
$WithinGroups$	0.066	18	0.004		
$Total$	0.066	19			

TABLE II

RANDOM EFFECTS ANOVA STUDY OF THE ACCURACY ON THE STERNBERG TASK PRE- AND POST-10HZ RTMS BY GROUP.

capacity of rTMS to modify performance on a cognitive task [5], [9], to our knowledge this is the first study to present data to show that 10Hz rTMS has a facilitatory effect on alpha spectral dynamics that predict working memory task performance. Finally, these results lend support to our argument regarding the plausibility of a developing a circuit based treatment model for memory impairment using TMS.

V. FUTURE WORK

The extent to which 10Hz rTMS directed to the subject-specific prefrontal node in the neural assembly sub-serving working memory performance cannot be determined from this study, but such knowledge would be important for future clinical applications of rTMS. We plan to address this question using functional magnetoencephalography (MEG) techniques to determine the subject-specific path engaged in task performance, and to also determine the extent to which stimulation of a principal node in this circuit is more effective than similar stimulation directed to the contra-lateral homologous cortex. Data collection for this arm of our study is in progress. The molecular substrate of the response to TMS in humans is not known. Hence, with colleagues in the University of Utah Department of Human Genetics, we plan to determine the extent to which variability in the response to 10Hz rTMS is at least in part, associated with polymorphism in candidate genes shown to modify working memory performance in healthy and impaired individuals. Studies aiming to combine multimodal datasets such as the TMS, EEG, MRI, and MEG arms in this study will require new visualization and data management techniques. These issues are currently being addressed by incorporating digital signal processing tools and the development of a novel database model into the VisTrails workflow management system [1]. In this regard, the collaboration of the University of Utah's Scientific Computing and Imaging Institute, Department of Psychiatry, and Center for Advanced Medical Technology has been essential. We plan to extend this interdisciplinary approach to create a novel environment for multimodal data storage and analysis.

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[1] http://www.vistrails.org

REFERENCES

[1] E. Angelakis and J. Stathopoulou. Electroencephalographic peak alpha frequency correlates of cognitive traits. *Neuroscience Letters*, 371(1):60–63, 2004.

[2] G. Bryson. Initial and final work performance in schizophrenia: cognitive and symptom predictors. *Journal of Nervous and Mental Disorders*, 191(2):87–92, 2003.

[3] J. Callicott, B. Verchinski, S. Marenco, M. Egan, and D. Weinberger. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *American Journal of Psychiatry*, 160(12):2209–2215, 2003.

[4] C. Clark, M. Veltmeyer, R. Hamilton, E. Simms, R. Paul, D. Hermens, and E. Gordon. Spontaneous alpha peak frequency predicts working memory performance across the age span. *International Journal of Psychophysiology*, 43(1):1–9, 2004.

[5] J. Ford, D. Mathalon, S. Whitfield, W. Faustman, and W. Roth. Reduced communication between frontal and temporal lobes during talking in schizophrenia. *Biological Psychiatry*, 51(6):485–492, 2002.

[6] M. Green, K. Nuechterlein, J. Gold, D. Barch, J. Cohen, S. Essock, W. Fenton, F. Frese, T. Goldberg, R. Heaton, R. Keefe, R. Kem, H. Kraemer, E. Stover, D. Weinberger, S. Zalcman, and S. Marder. Approaching a consensus cognitive battery for clinical trials in schizophrenia. *NIMH-MATRIC Conference to Select Cognitive Domains and Test Criteria*, 56:301–330, 2004.

[7] P. Harvey, M. Green, S. McGurk, and H. Meltzer. Changes in cognitive functioning with risperidone and olanzapine treatment: a large-scale, double-blind, randomized study. *Psychopharmacology*, 169(3–4):404–411, 2003.

[8] W. Klimesch. Eeg alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Research Reviews*, 29:169–195, 1999.

[9] W. Klimesch, P. Sauseng, and C. Gerloff. Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency. *European Journal of Neuroscience*, 17(5):1129–1133, 2003.

[10] E. Kraepelin. Compendium der psychiatrie. *A. Abel, 1883. Psychiatrie: Ein Lehrbuch fur Studierende und rtze.4th edition,. 1883.*

[11] S. McGurk, P. Harvey, R. LaPuglia, and J. Marder. Cognitive and symptom predictors of work outcomes for clients with schizophrenia in supported employment. *Psychiatric Services*, 54(8):1129–1135, 2003.

[12] A. Mishara and T. Goldberg. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. *Biological Psychiatry*, 55(10):1013–1022, 2004.

[13] G. Preston and D. Weinberger. Intermediate phenotypes in schizophrenia: a selective review. *Dialogues in Clinical Neuroscience*, 7(2):165–179, 2005.

[14] R. Rosenheck, S. Bingham, W. Liu-Mares, J. Collins, S. Warren, and D. Leslie. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. *JAMA*, 290(20):2693–2702, 2003.

[15] P. Sauseng and W. Klimesch. Eeg alpha synchronization and functional coupling during top-down processing in a working memory task. *Human Brain Mapping*, 26(1):148–155, 2005.

[16] L. Selemon and P. Goldman-Rakic. Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: application of a three-dimensional, stereologic counting method. *Journal of Computational Neurology*, 392(3):402–412, 1998.