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**ONR
FINAL REPORT**

Principal Investigator Dr. Marcel Adam Just
Institution: Carnegie Mellon University
Address: Department of Psychology, Pittsburgh, PA 15213
Phone: (412) 268-2791
Fax: (412) 268-2804
Email: just@cmu.edu
Web Page: <http://www.ccbi.cmu.edu>
Contract: N00014-10-1-0069
Project Title: *Brain Imaging and rTMS Studies of Individual Differences in Cognitive Processing*
Program Officer: Dr. Raymond Perez

Scientific and Technical Objectives:

This section has not changed since the previous report. The proposed research has the goal of understanding the brain system properties that underlie individual differences in cognitive performance and using this understanding to enhance performance of individuals and organizations. The proposed research will apply new leverage to this familiar problem using innovations in brain science from the past ten years that permit detailed noninvasive measurement of brain function, brain anatomy, and now the effect of magnetic brain stimulation, as they relate to cognitive performance. For example, the essence of fluid intelligence is the ability to adapt to a new task or problem. This ability cannot be characterized in simple behavioral terms such as “speed of processing.” In the new brain systems view, fluid intelligence consists of the ability to dynamically configure a new network (team) of brain areas that can effectively collaborate to perform a new task. The *individual differences* in fluid intelligence, according to this view, are underpinned by differences in this dynamic “network configuration” ability, which we call **adaptability**. This new approach, when used in the context of a suitable integrating theoretical framework, has the potential of determining the brain bases of individual differences in cognition.

We propose to investigate three properties of brain systems believed to underlie individual differences in cognition. They are network adaptability (mentioned above), network connectivity (inter-center communication), and neural efficiency (amount of brain resources required to perform a given task). We will use these measures to predict cognitive performance. Moreover, we will investigate whether it is possible to enhance cognitive performance by changing some of the underlying brain characteristics.

Approach:

The approach is to assess the brain function and cognitive performance in tasks during the unavailability induced by repetitive transcranial magnetic stimulation (rTMS) of a key cortical area that normally underpins a processing network. We will contrast that with processing in a less necessary cortical homologue. In a language task this may be Wernicke's area (Left Superior Temporal Gyrus) and the right hemisphere Superior Temporal Gyrus. We will learn how the brain system dynamically deals with the processing of a given level when a key network component (brain center) gradually becomes unavailable. We will be collecting brain activation measures (fMRI) during tasks that load on the temporarily unavailable region, as well as examining behavioral measures of performance.

Three tasks (sentence comprehension, discourse comprehension, and multitasking) are included in the progress report using well established sets of materials. In the sentence and discourse tasks, participants read cognitively demanding sentences that described an interaction between two characters. In the multi-task, participants listened to factual statements about general world knowledge that were either true or false. The factual statements were presented singly in one ear or two different items were presented to both ears at the same time. The adaptive nature of the language network in the brain was examined through the use of rTMS applied to critical regions of the cortex (Wernicke's or homologue). fMRI activation was acquired before and after rTMS was applied in all tasks, as well as during rTMS, while the participants were performing the sentence comprehension task in the scanner.

Concise Accomplishments:

The main accomplishment was the discovery of what happens neurologically and psychologically when a key brain area (Wernicke's area) is temporarily impaired by rTMS during the performance of a task. What occurs within seconds is a dynamic re-organization of the operating brain network, substituting the contralateral homolog area for the impaired one, and recruiting a new set of collaborating areas to form a new temporary network.

There were two outstanding facets of the subsequent brain adaption: synchronization changes in compensating contralateral RH (Right Hemisphere), medial frontal regions, and perilesional regions (i.e. adjacent to the area where rTMS was applied), as well as recovery processes in the regions downregulated by rTMS. The compensatory adaptation consisted of increased coordination between the right hemisphere homolog of the stimulation site (contralesional) and a medial frontal region, as well as between regions close to the stimulation site (perilesional) and the same frontal region of cortex. These findings reveal the principles by which a brain network is recruited to perform a given task, namely, new partnerships are formed among the most able currently available areas. This finding has implications for enhancing the range of cognitive capabilities in trainees and for the understanding and treatment of brain injury.

There were two interesting behavioral implications. Despite the previously-downregulated (impaired) regions gradually returning to their original levels, the compensating regions did not all phase out their activity, resulting in co-activity in the recovering original network and the newly recruited compensating network, probably accounting for the sustained and perhaps enhanced behavioral performance during and after rTMS stimulation. Furthermore, the degree of compensation and recovery in an individual was related to the individual's working memory capacity for language (measured as reading span or RSPAN), indicating a capacity for dynamic reorganization. This reporting period included a completion of the analyses procedures and writing of manuscripts to disseminate the knowledge gained in the project.

Expanded Accomplishments:

The research uncovered a set of common principles of brain adaptation to a “virtual lesion”, constituting a unified account of the enhanced behavioral performance that ensues.

- We found that performance could be enhanced following rTMS due to formation of new partnerships among compensating cortical regions following rTMS to a key node. This beneficial compensatory adaptation occurred by increasing synchronization between a peri-lesional site (a region adjacent to the rTMS-downgraded area) and the contralateral right hemisphere language regions as well as a cognitive monitoring region (medial frontal). A schematic description of how this increase in synchronization between peri-lesional regions and compensatory cortical regions might occur is shown in Figure 1.
- We determined that performance improved following rTMS to a primary language region (as indicated by faster response times) as a result of co-activity in the recovering original network and the newly recruited compensating network.
- There were individual differences in the degree of neural adaptability. Readers with larger working memory spans activated the compensating regions more than individuals with lower spans.

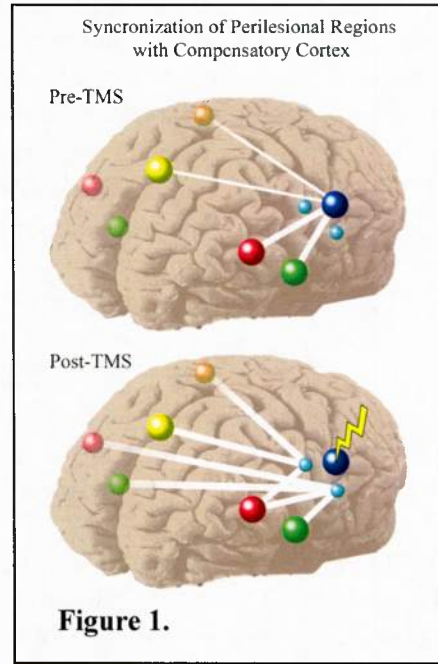


Figure 1.

Expanded data analyses were completed for all tasks during the reporting period. Write-up of the sentence processing project was completed (Mason et al., 2013) and continued for the dual task and the discourse comprehension project. The cognitive studies show an adaptive recruitment of compensating brain regions to perform a task when the usual network is not available. The *improvement* in performance as a result of this adaptive recruitment offers a promising new direction for developing digital learning methods to enhance the performance. Furthermore, the adaptive recruitment was a function of the working memory capacity of the individual during reading (RSpan). The individual-dependent cortical compensation to recover from the rTMS led to greater improvement in performance, suggesting new investigations of performance prediction and directions in individual-oriented training. The capacity-based adaptation also indicates potential new directions for intervention with victims of traumatic brain injury.

1. *Cortical reorganization induced by rTMS during sentence comprehension.* fMRI-measured activation was examined as participants read sentences describing a straightforward interaction between two people (adapted from Just et al., 1996) and answered true-false probes following those sentences. They read sequences of sentences before, during, and after rTMS was applied to the left posterior superior temporal gyrus (Wernicke’s area) and its right hemisphere homologue. The objective was to determine what regions of differentially specialized cortex would be adaptively recruited following the down-regulation of a critical language cortical center.

The main adaptive response to the impairment of Wernicke’s area by rTMS was the synchronized activation of a network of newly recruited compensating brain areas. This finding demonstrates the dynamic recruitment of a compensatory network whose membership is determined by their

information processing capabilities. Although thousands of brain imaging studies have reported which set of brain areas activate in a given task, no one has examined the principles by which this set is dynamically determined. By disabling a key member of a language processing network while it is in use, we revealed for the first time that the system recruits the most appropriate available brain resources to meet an information processing need.

This first characterization of the brain's adaptation to a temporary unavailability during a language task provides a model of the brain's naturally occurring response to brain trauma, such as a stroke-induced focal lesion or a traumatic brain injury. The findings provide valuable new knowledge of compensatory and recovery mechanisms that should be useful for the cognitive rehabilitation treatment of traumatic brain injury, stroke, and other trauma that disables a cortical region. Indicating that:

- Impairing an activating brain area evokes a synchronized compensating network
- Impairing a cortical center shifts processing to contralateral and perilesional areas
- rTMS impairment of an activating region also impairs distal regions that were partnering with the impaired region
- Contralateral activation and better performance correlate with working memory capacity

The findings also address some of the recent issues of public interest associated with concussion and Traumatic Brain Injury (TBI). The work here outlines the nature of changes that spontaneously occur in response to impairment, providing a new perspective on the relatively unexplored area of dynamic recovery in response to brain injury.

2. *Cortical reorganization induced by rTMS during intentionality comprehension.* This study is like the first except that the go-to backup area (the right homolog of Wernicke's area) was already engaged in the task. This right homolog of Wernicke's area is central to theory of mind/intentionality computations that occur during the comprehension of a narrative text. Theory of mind (ToM) computations are spontaneously invoked to understand a character's intentions and goals, as shown by several fMRI studies (e.g., Mason & Just, 2011) indicating the association of this area with ToM. Participants read passages such as: *Brad had no money but he just had to have the beautiful ruby ring for his wife. Seeing no salespeople around, he quietly made his way closer to the ring on the counter. He was seen running out the door.* How would the partnerships among brain areas shift after the application of rTMS to Wernicke's area when its contralateral homolog was already being used for intentionality comprehension?

The main adaptive response to impairment of Wernicke's area was a recruitment of a compensatory network that again included the region adjacent to the rTMS site, as well as the recruitment of its right hemisphere homolog (which is anterior to the area activated by ToM computations). (Another partner in the compensatory network was the medial frontal region).

Thus the compensatory recruitment principle when an area is impaired is *Recruit the contralateral homolog, but if it is already activated/engaged, recruit an adjacent (presumably similarly specialized) area.*

These new partnerships again resulted in an improved behavioral response (faster reading times as shown by the blue line in Figure 2). As in the sentence comprehension task, enhanced performance arose out of co-activity of the newly developed compensatory partnerships and the re-emergence of the primary regions.

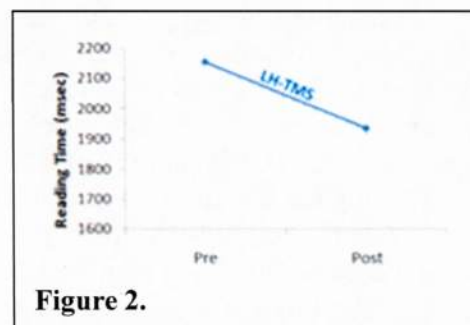


Figure 2.

3. *Cortical reorganization induced by rTMS during multitasking (listening to two people speak at the same time).* This experiment was developed to examine cortical adaptability in a task that pushed individuals to the upper limit of cognitive abilities. The ability to process two streams of information at the same time in the same modality is a difficult yet highly useful ability. Here a simple task in which people listened to factual sentences (*During leap years, February has 29 days, and this occurs once every four years*) was contrasted with a complex dual task in which they heard two different sentences presented simultaneously, one to each ear. The study thus examined whether rTMS could evoke an adaptive compensatory network in the dual condition, where there are few spare resources available. (Recall that in the sentence task, the degree of adaptation was correlated with an individual's working memory capacity).

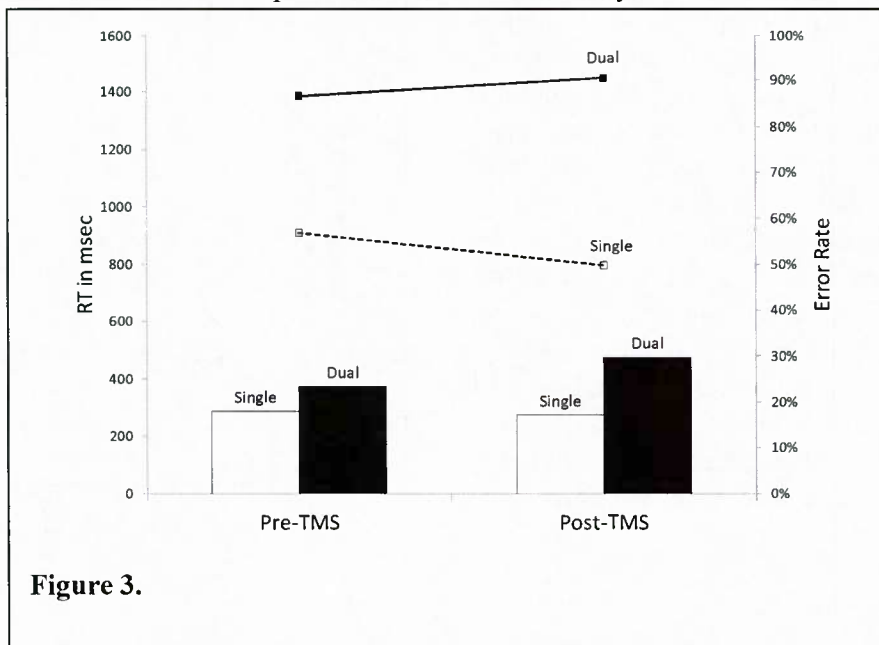


Figure 3.

rTMS applied to Wernicke's area in the dual task condition failed to evoke an adaptive response. Behaviorally, there was an increase in errors and in response time following rTMS, as shown in Figure 3. (The results for the single task (or single sentence) condition resembled the study in which single sentences were presented).

Thus the principles for network adaptation to impairment appear not to apply when the system is already in a high resource-consumption state. This is a second indication (in addition to the individual differences correlation between working memory capacity and amount of adaptation) the recruitment of an alternative compensatory network is resource-dependent, as further described below.

4. *Cortical synchronization of peri-lesional regions and compensating regions (primarily contralateral) is correlated with working memory capacity.* In all three tasks, a common pattern emerged that indicated rTMS compensation was a function of individual differences in working memory capacity. In the sentence comprehension task, additional analyses completed in this period suggest that this neural adaptation was a function of an individual's working memory span; higher span subjects had a greater recruitment of the contralateral region than did lower span subjects in the compensating RH regions (shown in Figure 4).

Similarly, in the intentionality/narrative comprehension task, the neural adaptation was also a function of an individual's working memory span.

Perhaps the most striking response to rTMS was the greater adaptability demonstrated as working memory capacity increased during the complex dual-task. The higher the working memory capacity of the individual was, the greater was the likelihood of an increase in coordination between the the contralateral regions for the more complex dual task as compared to the single channel task ($r = 0.41$; see Figure 5). This

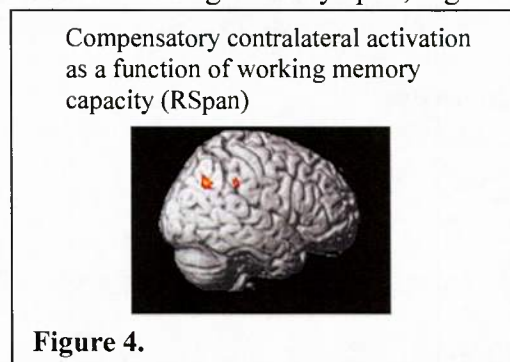
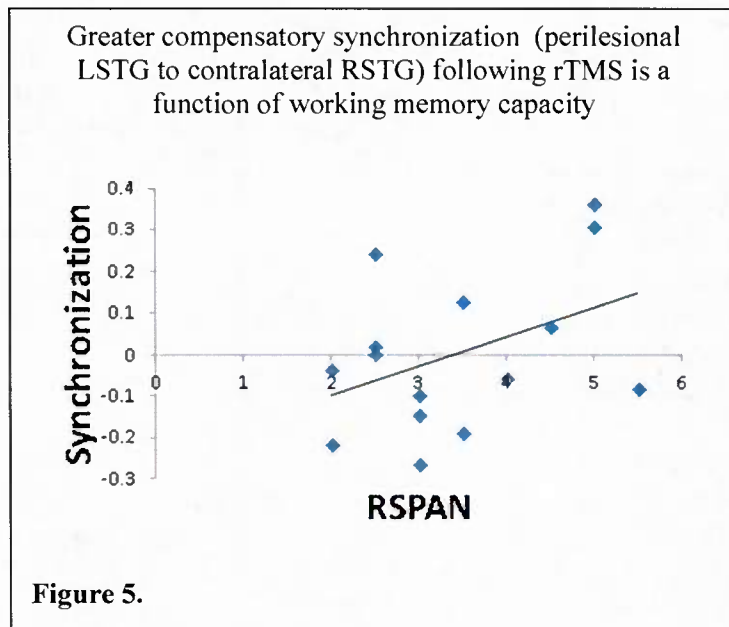


Figure 4.

pattern of results across three varied tasks indicates that adaptability increases with the working memory capacity of an individual.

This completes the principles of network adaptation derived from this project. They indicate the fundamental way that cognitive systems are dynamically configured. The principles also indicate a potential for improved instructional and performance outcomes by using two networks in tandem, and that this approach should be particularly applicable to individuals with higher working memory capacities. They also indicate a specific approach to treatment methods for traumatic brain injury. In summary, rTMS in conjunction with fMRI has provided an invaluable and unique insight into how the components of human intelligence are assembled denovo each time we face a new situation.



Work Plan:

Transition to new ONR project (N000141310250). Continued submission of manuscripts based on data acquired during the project.

Major Problems/ Issues (if any): None.

Technology Transfer:

We have developed and maintain contact with other laboratories using rTMS in the scanner to share our approach to the comfort issue. This contact was utilized to establish the efficiency of TMS coil positioning in the scanner. Additionally, we shared knowledge of possible interactions of the TMS coil and auditory stimuli delivery methods. We have enabled another lab at Carnegie Mellon University to examine learning and performance using techniques developed in our rTMS projects.

Foreign Collaborators and Supported Foreign Nationals: N/A

Productivity:

Refereed Journal Articles:

Mason, R. A., Prat, C. S., & Just, M. A. (2013). Neurocognitive brain response to transient impairment of Wernicke's area. *Cerebral Cortex*; doi: 10.1093/cercor/bhs423

Buchweitz, A., Keller, T. A., Meyler, A., & Just, M. A. (2012). Brain activation for language dual-tasking: Listening to two people speak at the same time and a change in network timing. *Human Brain Mapping*, 33, 1868-1882.

Workshops and Conferences:

A concurrent transcranial magnetic stimulation (TMS) and fMRI investigation of cortical adaptation and behavioral improvement during sentence comprehension. Poster presented at the 18th Annual Meeting of the Cognitive Neuroscience Society, April 2-5, 2011, San Francisco, California.

Identifying and characterizing individual concepts from their brain activation signatures: How the brain represents meaning. Triple Helix Organization Lecture at Carnegie Mellon University, November 3, 2011, Pittsburgh, Pennsylvania.

Neuroscience perspectives on comprehension of literal and figurative language. Keynote address given at the International Society for the Empirical Study of Literature and Media (IGEL) Conference, July 7-10, 2012, Montreal, Quebec, Canada.

Changing brains for changing times. Distinguished Scientific Contribution Award Address given at the 22nd Annual Meeting of the Society for Text & Discourse, July 10-12, 2012, Montreal, Quebec, Canada.

Decoding individual concepts from their brain activation signature, in neurotypicals and in autism. University of Pittsburgh, Department of Psychiatry Lecture Series, September 14, 2012, Pittsburgh, Pennsylvania.

The neurocognitive basis of knowledge acquisition: Building better brains. Office of Naval Research Principal Investigators' Meeting, Arizona State University, September, 18-19 2012, Tempe, Arizona.

Awards/Honors:

2012 Distinguished Scientific Contribution Award from the Society for Text and Discourse to PI
2013 Appointment as University Professor at Carnegie Mellon



Center for Cognitive Brain Imaging

Marcel Just
D. O. Hebb Professor
Carnegie Mellon
Department of Psychology
Pittsburgh, PA 15213
Email: just@cmu.edu
Tel: (412) 268-2791
Fax: (412) 268-2804
<http://www.ccbi.cmu.edu/>

9 August, 2013

To Whom It May Concern,

Enclosed is the Final Technical Report for the ONR research grant entitled, *Brain Imaging and rTMS Studies of Individual Differences in Cognitive Processing*, Contract Number N00014-10-1-0069. The report covers the grant period of 12/01/09 to 01/31/13.

Sincerely,

A handwritten signature in blue ink that reads "Marcel Just". The signature is stylized and cursive.

Marcel Just
Director
Center for Cognitive
Brain Imaging

MJ/pw

Enclosure