Brenda Milner

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2009 Balzan Prize for Cognitive Neurosciences

For her pioneering studies of the role of the hippocampus in the formation of memory and her identification of different kinds of memory system.

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Hemispheric Interaction in Cognitive Processes

Pioneering work by Dr. Brenda Milner and her colleagues has long established the important distinctions in functions of the left and right hemispheres of the human brain. Although language dominance in the left hemisphere had previously been established, her team used specific memory tasks in patients with damage to one side of the brain to demonstrate equally important, complementary specializations of the right hemisphere for visuospatial and other non-verbal information. However, the *integration* of information between the two is required for adequate memory processing. Through her careful study of patients who have undergone commissurotomy for the relief of intractable epilepsy, Dr. Milner has demonstrated that each hemisphere, when acting alone, is severely limited in its capacity to encode and retain information successfully, thus highlighting the critical contribution of interhemispheric communication for normal memory function. The research project funded with the Balzan Prize awarded to Dr. Milner aims to illuminate the nature of hemispheric interaction in the human brain and how the integration of information between the two hemispheres enables remembering. To this end, we will combine fine-grained behavioural paradigms with conventional functional magnetic resonance imaging (fMRI) experiments as well as newly emerging tools in fMRI that allow us to examine patterns of interaction between distant brain regions. In a large cohort of healthy young subjects, we plan to

study how individual differences in patterns of hemispheric connectivity relate to the natural variation we see in capability for different types of memory tasks and to the cognitive strategies adopted by each individual.

One important component of this project will be the resting-state fMRI paradigm, which takes advantage of the natural patterns of fluctuations in the brain activity at rest. In particular, brain regions that normally work together during cognitive tasks are tightly coupled in their activity patterns in the absence of any external task requirement. In recent years, this discovery has led to an explosion of studies investigating the correlated activity of the resting brain to study functional interactions, and has contributed to a new understanding of intrinsic network organization of the brain. Dr. Randy Buckner's research team at Harvard is one of the world leaders in this new field. Of particular interest to Dr. Milner's research project, he and his colleague, Dr. Hesheng Liu, have used the approach to investigate the asymmetry of connectivity patterns in the right and left hemispheres. They have offered to lend their technical expertise to apply their method to examine the individual differences in the intrinsic connectivity architecture within and between the two hemispheres. As the first step of this collaborative effort, one of Dr. Milner's postdoctoral fellows spent the summer of 2012 at Dr. Buckner's lab at Harvard to learn how to use the analysis tools they had developed for the resting-state fMRI data. Soon after the second postdoctoral fellow joined the lab in October 2012, both attended a Functional Connectivity workshop offered by the Martinos Center for Biomedical Imaging in Boston to further explore the different approaches available to study brain interactions.

Dr. Milner's team is currently in the final stages of testing a preliminary sample of twenty subjects on a paradigm to assess the role of interhemispheric connectivity in memory. Although interhemispheric connectivity-strength between the two hippocampi predicts individual differences in memory performance for dually encodable (i.e., visuospatial and verbal) objects, it is unclear if this connectivity reflects integration of visuospatial and verbal information, or whether interhemispheric connectivity is related more generally to memory performance, regardless of the type of information being processed. To investigate this question, twenty healthy, right-handed subjects are presented with ninety concrete and ninety abstract words. Subjects provide an imageability rating, indicating how easily they can visually imagine the word (i.e., to assess integration of verbal and visuospatial information). This task is followed by an out-of-scanner recognition memory test. Subjects also undergo a resting-state fMRI scan to assess intrinsic interhemispheric connectivity differences between in-

dividuals and how they relate to variation in neuropsychological measures of verbal and nonverbal memory.

In the task fMRI, strength of hemispheric interaction between the hippocampi should correlate with performance on a recognition memory test for stimuli presented in the scanner, in line with previous studies. Further, we predict that if interhemispheric hippocampal connectivity in memory encoding is related to the integration of verbal and visuospatial information, we should observe increased interhemispheric connectivity in the hippocampi for highly imageable concrete items (involving both verbal and visuospatial processing) that were subsequently remembered, compared to low-imageable abstract items (primarily involving verbal processing) that were subsequently remembered. In contrast, conditions that require predominantly verbal processing (i.e., low imageability abstract) should involve a more lateralized network.

Resting-state scans will be used to examine how individual differences in intrinsic interhemispheric connectivity relate to integration of visuospatial and verbal information, memory performance on our task and standardized neuropsychological measures. In particular, individuals with high intrinsic hemispheric connectivity should display greater integration of visuospatial and verbal information relating to superior subsequent memory performance, as well as enhanced performance on standardized neuropsychological memory measures compared to individuals exhibiting less connectivity during resting state. Thus, this work builds upon classical neuropsychological observations of split-brain patients with the use of novel, cutting-edge neuroimaging techniques. Findings will be presented at the Society for Neuroscience meeting in Washington, DC in November 2014.

In addition to the aforementioned project, Dr. Milner's lab is developing several other memory paradigms to understand fully the nature of interhemispheric connectivity:

(1) Subjects will be presented with a pair of pictures of common objects. In one condition, subjects will be asked to combine the pair in a mental image, emphasizing the visual quality of the association. In another condition, they will be asked to generate a sentence using verbal labels for the pictures, in order to encourage integration of verbal description with the visually presented stimuli.
(2) Another test will use meaningful adjective-noun pairs that differ in the degree of imageability. For example, memory for association between highly imageable combinations, such as "green" and "book", will be contrasted with meaningful but more

abstract associations, such as “engaging” and “book”. Processing of highly imageable word pairs has been shown to recruit both right and left hemispheres, while processing of abstract pairs depends more on the left-lateralized language network.
(3) Subjects will study name-name or face-face pairs, which are expected to depend primarily on left- or right-lateralized memory structures, respectively. The subjects will then learn name-name and face-face associations together, so that the facilitation of name-pair learning in the presence of associated visual information or the face-pair learning in the presence of associated verbal information can be measured.

To summarize, Dr. Milner’s lab is (1) gaining experience in relevant neuroimaging methods through workshops and collaborative interaction with the Harvard team; (2) running and analyzing a preliminary sample of 20 subjects; and (3) designing behavioural paradigms for future task-fMRI experiments. These are critical steps for carrying out this innovative and large-scale study.

Researchers:
Dr. Randy Buckner
Dr. Joelle Crane
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Two Post-doctoral fellowships:
Meera Paleja, PhD Ryerson University, Toronto 2012
Ami Tsuchida, PhD McGill University 2012