Correlation Modulation Networks to Assess Changes in Functional Connectivity with Task Difficulty

M. S. Korgaonkar[1], S. Fiore[2], C. J. Perkins[2], N. K. Squires[3], Z. Yan[4], and M. E. Wagshul[1,4]

[1]Biomedical Engineering, Stony Brook University, Stony Brook, NY, United States, [2]Neurology, Stony Brook University, Stony Brook, NY, United States, [3]Psychology, Stony Brook University, Stony Brook, NY, United States, [4]Radiology, Stony Brook University, Stony Brook, NY, United States

Introduction

The primary role of functional imaging studies, from time of their advent, has been to determine the brain regions in which the measured signal varies in response to manipulation of experimental conditions. Regions identified by these manipulations are in general considered as components of a network associated with the experimental conditions. However, these analyses are limited in deducing how the links between these components are manipulated with the experiment. Functional (psycho-physiological interactions [1], correlation modulation [2]) and effective connectivity (Dynamic causal modeling, Structural Equation Modeling [3]) methods developed over the last few years have enhanced our understanding of components of brain networks and their interactions. While both types of methods tell us about the modulation of the links in the networks with experimental conditions, only effective connectivity methods contain information about the directionality of interactions. Our previous results show that there is differential recruitment of brain regions in a task difficulty modulated verb generation task. Using the correlation modulation approach, we sought to evaluate the following: 1. If the connectivity between language regions is modulated by experimental conditions – particularly between generating verbs as compared to passive viewing of non-words and difficult as compared to easy to generate verbs; and 2. How these condition-specific modulations of connectivity differ between young and old subjects.

Methods

10 young (5 females; mean age, 24.4 ± 5.8yo) and 10 old (5 females; mean age, 57.8 ± 8.7yo) healthy volunteers participated in this study. All subjects were right handed and native English speakers. Subjects performed a verb generation task during which nouns were flashed on the screen one at a time, silently generated a verb associated with each word and pressed a button immediately following completion of each task. Subject response times were recorded and used to categorize stimuli into *easy* or *difficult categories.* Non-words, which served as the control task, were also randomly shown. (For details about the task, easy-difficult categorizations and MRI sequence parameters, see [4]). Correlation modulation (CM) networks were generated for "All words vs. control" and "Difficult vs. Easy" for both the young and old subjects. The steps for generation of CM networks were as follows:

ROI Selection: Based on prior language functional neuroimaging studies, the following *apriori* cortical ROIs were used (left-L and right-R): BA44 (pars opercularis), BA45 (pars triangularis), BA47 (pars orbitaris), inferior temporal gyrus (ITG), middle temporal gyrus (MTG), superior temporal gyrus (STG), supramarginal gyrus (SMG), angular gyrus (AG) and the anterior cingulate cortex (ACC). Next, subject-specific functionally activated clusters within the anatomical ROI for the "All words vs. Control" condition were defined (uncorrected, $p<0.05$). The principal eigenvariate in the largest cluster within the ROI was used to extract the fMRI time-course.

Condition specific networks: Functional connectivity networks for a particular condition were generated by computing a weighted correlation between the time-courses of every pair of the defined ROIs. All ROI paired correlations were carried out at the neuronal level after generating the neuronal time-series by using a Parametric Empirical Bayesian formulation for hemodynamic de-convolution of the fMRI time-course [5]. The weighting for the correlation is condition dependent and hence results in a network specific to the condition. The weighted correlation between two regions with time-courses $x = (x_1,..,x_n)$ and $y = (y_1,..,y_n)$ is given by:

$$c_p(x,y) = \frac{\mathrm{cov}_p(x,y)}{\sqrt{\mathrm{var}_p(x)\,\mathrm{var}_p(y)}} \quad \textit{where,}\ \ \mathrm{cov}_p(x,y) = \sum_{t=1}^{n} p_t x_t y_t \ \ \&\ \ \mathrm{var}_p(x) = \mathrm{cov}_p(x,x)$$

and $p = (p_1,..,p_n)$ is the condition-specific weight function (one for condition present and zero elsewhere).

CM Networks: Next, a CM network, showing variations in functional connectivity between two conditions, was obtained by subtracting the respective pair-wise correlation values between the two conditions. This subtraction removes artifactual correlation confounds due to cardiac, respiratory or MR noise, which are all common to both conditions.

Statistical Analysis: Each component of the CM network was tested for significance across subjects using the Wilcoxon signed rank test. Comparison of CM networks between the young and old groups were done using the Wilcoxon rank sum test. Network links were considered significant at 5% level of significance.

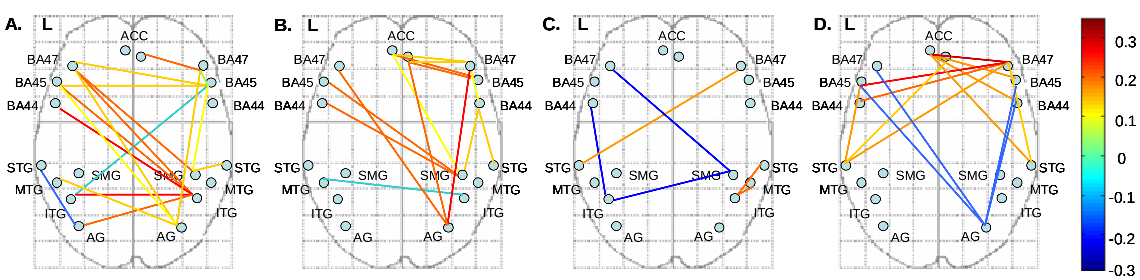

Fig1.CM networks: All words vs. Control (A – Young; B – Old) and Difficult vs. Easy (C – Young; D – Old). Mean CM value over the group is indicated by color of the links (see color scale)

Results

There were differences in functional connectivity for both generation of verbs as compared to passive viewing of controls (Fig 1 A&B) and for difficult as compared to easy generation of verbs (Fig 1 C&D). Functional interaction was also different between the young and old groups for the two comparisons. Between the young and old group, functional interactions between the L & R-ITG and between L-AG & R-ITG were found to be significantly different for the "All words vs. Control" network. For the "Difficult vs. Easy" network, the two groups interacted differently between L-BA44 & L-BA45, L-BA44 & L-MTG, L-ACC & R-BA47 and R-BA44 & R-AG.

Discussion

Evaluating differences in functional interaction can give further insight into understanding how the brain responses to modulation of task difficulty and how these interactions vary with subject age. We found clear differences in inter-hemispheric and frontal-temporal connectivity between the age groups. Like all functional connectivity methods, this method is limited to only modulation of connectivity with no information about directionality. However, the results from these analyses, could aid in driving the analyses of effective connectivity, which require the definition of a network model and its components.

References

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