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A network approach to fMRI condition-dependent cognitive activation studies as applied to understanding sex differences

Tracy Butler [a,*], Hong Pan [a], Julianne Imperato-McGinley [b], Daniel Voyer [c], Amy Christine Cunningham-Bussel [a], Juan J. Cordero [b], Yuan-Shan Zhu [b], David Silbersweig [a], Emily Stern [a]

[a] *Functional Neuroimaging Laboratory, Department of Psychiatry, Weill Medical College of Cornell University, Box 140, Room F1311, 1300 York Avenue, New York, NY, USA*

[b] *Department of Endocrinology, Weill Medical College of Cornell University, New York, NY, USA*

[c] *Department of Psychology, University of New Brunswick, Fredericton, NB, Canada*

Abstract

Network approaches to analysis of functional neuroimaging data provide a powerful means with which to understand the complex functioning of the brain in health and disease. To illustrate how such approaches can be used to investigate sex differences in neurocognition, we applied the multivariate technique of Principal Components Analysis (PCA) to an fMRI dataset obtained during performance of mental rotation – a classic visuospatial task known to give rise to sex differences in performance. In agreement with prior results obtained using univariate methods, PCA identified a core mental rotation network (principal component [PC]1, accounting for 53.1% of total variance) that included activation of bilateral frontal, parietal, occipital and occipitotemporal regions. Expression of PC1 was similar in men and women, and was positively correlated with level of education. PC2, which accounted for 5.7% of total variance, was differentially expressed by men and women, and indicated greater mental rotation-associated neural activity in women in such high-order cortical regions such as prefrontal cortex and superior parietal lobule, in accord with prior findings, and with the idea that women may take a more "top-down" approach to mental rotation. By quantifying, in a data-driven fashion, the contribution of factors such as sex and education to patterns of brain activity, these findings put the magnitude of neural sex differences during mental rotation into perspective, confirming the commonsense notion that, as humans, men and women are more alike than they are different, with between-individual variability (such as level of education, which, importantly, is modifiable) generally outweighing between-sex variability. This work exemplifies the role that multivariate analysis can play in identifying brain functional networks, and in quantifying their involvement under specific conditions and in different populations.

Keywords: Sex; Gender; Principal components analysis; PCA; Multivariate; fMRI; Functional neuroimaging; Network; Visuospatial; Mental rotation; Cognitive; Education

1. Introduction

Prior studies using FDG PET and SPECT to investigate brain functional networks have focused on the brain in a resting state. Imaging methodologies with better temporal resolution such as fMRI allow scanning to occur not only at rest, but also while subjects are performing a specific task designed to activate particular brain regions or circuits of interest. Combining such activation studies with multivariate and other network analysis approaches provides a powerful means with which to understand the complex functioning of the brain in health and disease. Here, we describe the application of Principal Component Analysis (PCA) and complementary approaches to understanding sex differences in cognition.

* Corresponding author. Tel.: +1 212 746 3766; fax: +1 212 746 5818. *E-mail address:* tab2006@med.cornell.edu (T. Butler).

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Whether men and women differ in their thinking styles and/or abilities is a controversial topic of great interest to neuroscientists as well to the lay public. Sex differences are also important in the context of many medical and psychiatric disorders which have a different incidence or course depending on sex. An increasing number of functional neuroimaging studies document sex differences during the performance of various cognitive and emotional tasks (for review see [1]). Based on these studies, it is clear that participant sex must be considered when designing functional neuroimaging studies and interpreting results. What remains less clear is the precise nature and magnitude of sex effects; even using a well-studied paradigm such as mental rotation [2] (a visuospatial task known to give rise to robust sex differences in performance), reported functional neuroanatomical sex differences have been variable [3–7], or absent [4,8,9], though greater frontal activity in women has been found in the majority of studies [3,6,10], including one from our group [11]. While much of this variability is likely due to different experimental paradigms and methods of analysis, it must be acknowledged that some variability is likely due to the moderate size of the sex effect, as well as to non-systematic differences in performance strategy. Certainly, as humans, men and women are more alike than they are different, with between-individual variability (such as education levels) generally outweighing between-sex variability. It is a limitation of functional imaging studies using categorical analyses (contrasting men to women) that only those differences highly localized in space are detected.

Multivariate methods such as Principal Component Analysis (PCA) provide a means to quantify the contribution of factors such as sex to patterns of brain activity in terms of the relationship between brain regions/networks, without deciding beforehand which factors are relevant. PCA enables decomposition of a collection of three dimensional, voxel-wise condition-dependent effect images of participants (be it a single group or multiple groups) into a cascade of uncorrelated component images, in descending order based on how much variation in the data is explained at each stage, where a projection direction is pursued to maximize the variation in the remaining data being expressed based on the covariance structure of the effect image collection. The resulting loading scores of each component image (i.e., eigenimage or spatial mode), which define the amount of contribution to this specific component image from each participant, can then be examined against various factors of interest (such as demographic indices and clinical scores). Related analyses of resting state data by Eidelberg and associates (e.g. [12,13] and other review articles in this issue) have provided important, clinically-relevant information concerning Parkinson's disease and other movement disorders.

In the study described below, we applied PCA to an existing fMRI dataset [11,14] to examine the contribution of sex and other factors (age, education, performance accuracy, reaction time, perceived task difficulty) to distributed patterns of brain activity. We discuss aspects of PCA relevant specifically to condition-dependent activation studies, and compare PCA results to previously-reported results [11] obtained using standard voxel-wise univariate factorial repeated-measures ANOVA. We also discuss a complementary voxel-wise measure of functional connectivity between an investigator-designated "seed" region and the rest of the brain, and how results obtained using such a thresholded correlational approach [15] differ from those obtained using PCA and related approaches. Potential uses for network approaches to cognitive and clinical neuroscientific problems are discussed in this context.

2. Materials and methods

fMRI datasets from 25 healthy, right-handed subjects [13 women (mean age 28.6, std 7.5); 12 men (mean age 30.1, std 5.9)] were analyzed for this study, which was approved by the Weill-Cornell Institutional Review Board.

2.1. Task

Using a validated, computerized version of the classic Shepard and Metzler mental rotation task [2,16], cube figures were presented in pairs (Fig. 1). Stimuli pairs were either the same, but rotated with respect to one another ("same" trials) or they were mirror images of each other ("different" trials). Stimuli were rotated by either 40°, 80°, 120° or 160°. Participants were instructed to mentally rotate figures into alignment in order to decide if they were the same or different. Accuracy and reaction time (RT) were recorded. An active control condition consisted of pairs of figures which were either identical or mirror images which were *not* rotated with respect to one another. Stimuli were presented in five-trial blocks, interspersed with a resting baseline condition (visual fixation). Additional details of this paradigm are available elsewhere [11,16]. After scanning, subjects completed a questionnaire about their experience and marked a 10 cm visual analog scale labeled "easy" and "hard" at each end. Average accuracy (proportion of correct responses) and reaction time for correct trials were calculated for each subject.

2.2. Image acquisition

Image data were acquired on one of two identical GE Signa 3 T MRI scanners (max gradient strength 40 mT/m, max gradient slew rate 150 T/m/s; General Electric Company, Waukesha, WI) using blood oxygen level dependent (BOLD) fMRI. Approximately equal numbers of men and women were scanned on each scanner. After shimming to maximize homogeneity, a series of fMRI scans was collected using gradient echo echo-planar imaging (EPI) (TR = 2000 ms; TE = 30 ms; flip angle = 70°, FoV = 240 mm; 27 slices; 5 mm thickness with 1 mm inter-slice space; matrix = 64×64). Images were acquired over the whole brain parallel to the AC–PC plane. The first six volumes of each epoch were discarded. A reference T1 weighted anatomical image with the same slice placement and thickness and a matrix of 256×256 was acquired immediately preceding the EPI acquisition. This high-resolution T1 weighted anatomical image was acquired using a spoiled gradient recalled (SPGR) acquisition sequence with a resolution of $0.9375 \times 0.9375 \times 1.5$ mm^3.