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

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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.

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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.

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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.

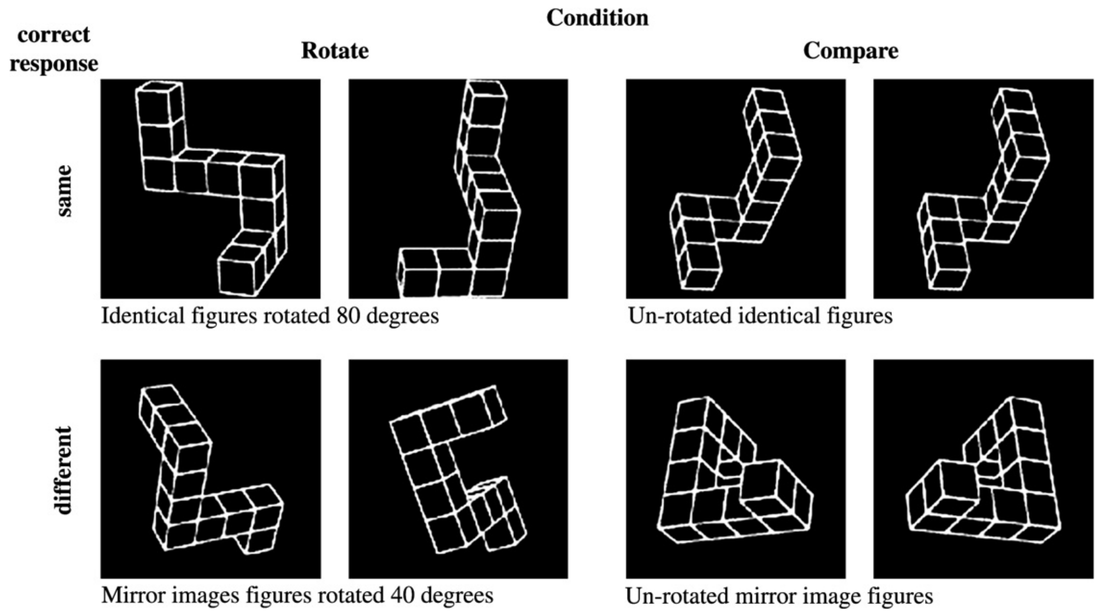

Fig. 1. Examples of mental rotation stimuli. Participants were instructed to mentally rotate pairs of figures into alignment in order to decide if they were the same or different. This figure was taken from [11] and used with publisher's permission.

2.3. Image processing and analysis

Image processing performed within a customized Statistical Parametric Mapping (SPM99) software package (www.fil.ion.ucl.ac.uk/spm) included manual AC–PC re-orientation of all anatomical and EPI images; realignment of functional EPI images based on intracranial voxels to correct for slight head movement between scans; co-registration of functional EPI images to corresponding high-resolution anatomical image for each participant; stereotactic normalization to the standardized coordinate space of Talairach and Tournoux (Montreal Neurological Institute, MNI average of 152 T1 brain scans) based on the high-resolution anatomical image; and spatial smoothing of the normalized EPI images with an isotropic Gaussian kernel (FWHM = 7.5 mm).

First, a voxel-by-voxel univariate multiple linear regression model at the participant level was employed to determine the extent to which each voxel's activity correlated with the condition-dependent principal regressors, which consisted of stimulus onset times and duration convolved with a prototypical hemodynamic response function. The temporal global fluctuation estimated as the mean intensity within brain region of each volume was removed through proportional scaling. The first-order temporal derivative of the principal regressors, temporal global fluctuation, realignment parameters, and scanning periods were incorporated as covariates of no interest. This first level analysis resulted in a set of contrast images of condition-dependent effects for each participant (including the effect of each condition vs. rest and the effects of between-condition comparisons), which were entered into second stage group-level analyses. These second level analyses included: (1) voxel-wise factorial repeated-measures ANOVA (previously reported in [11]); (2) block-level functional connectivity analysis through voxel-wise analysis of correlation with a functionally-defined seed region (also previously reported in [11]); and (3) PCA (newly reported here).

The voxel-wise repeated-measures ANOVA focused on direct, between-group categorical comparison of females versus males using the Rotation (vs. Rest) contrast. The block-level functional connectivity seed analysis identified brain regions that correlated with a single "seed" region of interest. This seed region was identified by assessing (in men and women separately) which brain regions correlated with mental rotation performance. In women, a region of dorsalmedial prefrontal cortex was most correlated with mental rotation performance. In men, a region of posterior insula (corresponding anatomically to parieto-insula vestibular cortex – PIVC) was most correlated with accurate mental rotation performance. Block-level activity in these seed regions was extracted and entered into separate multiple regression analyses for men and women to identify brain networks associated with accurate mental performance. See [11] for details of these analyses.

For the second stage group-level PCA, three sets of PCA (within either female or male group and with all 25 participants) were carried out to examine the major spatial modes of each condition/contrast effect in association with factors including education level, performance accuracy, perceived task difficulty level, reaction time, age and sex (the last factor was for PCA with all subjects only). For each condition/contrast, the normalized data matrix $X_{N\times M}$ (N participants under consideration, by M voxels within the standardized brain space) of a condition-dependent effect of interest (e.g. Rotate, or Rotate vs. Compare) was subject to singular value decomposition in the form of

$$X_{N\times M} = U_{N\times N} \cdot S_{N\times N} \cdot V^T_{N\times M},$$

where the N columns of unitary orthogonal $V_{M\times N}$ are the resulting eigenimages (spatial modes or principal components) of the correlation matrix $X^T_{M\times N} X_{N\times M}$ (i.e., pair-wise/voxel-to-voxel functional connectivity matrix), $S_{N\times N}$ is a diagonal matrix of decreasing singular values (i.e., $S^2_{N\times N} = V^T_{N\times M} \cdot X^T_{M\times N} \cdot X_{N\times M} \cdot V_{M\times N}$ is a diagonal matrix of decreasing eigenvalues) and the N columns of unitary orthogonal $U_{N\times N}$ are the corresponding loading score vectors. The first few eigenimages that covers 90% of the total variance are examined, the relation between the corresponding loading vector for each eigenimage and the factors of interest is tested through correlation and thresholded at $p < 0.05$ to reveal statistically significant association between a spatial mode and a behavioral/demographical measure.

3. Results and discussion

3.1. Behavioral results

As reported in detail in [11], reaction times were longer and accuracy lower at higher angles of rotation, in accord with Shepard and Metzler classic findings [2], confirming that subjects were appropriately engaged in the task. There were no significant sex differences in accuracy or reaction time. Women averaged 75% correct (std 16), men 83% correct (std 17). Similar levels of behavioral performance among males and females – not unexpected given the low sample size typical of this and most functional neuroimaging studies – allow interpretation of imaging results without the confound of differential performance. The absence of behavioral sex differences can be ascribed with greater confidence to low statistical power, since prior extensive behavioral testing has shown the mental rotation task used in this study to be a valid measure of mental rotation abilities which does in fact give rise to the expected male performance advantage when applied to a larger population [16]. Thus, our finding of non-significant behavioral sex differences during fMRI scanning does not call into question the validity of the task or subjects' engagement in the task, but instead lends support to the idea that significant sex differences in patterns of neural activity may be due to basic differences in processing, and not solely to differential performance.

3.2. Categorical analyses (voxel-wise factorial repeated-measures ANOVA): Rotate vs. Control condition; Men and Women combined

As reported in detail in [11] and shown in Fig. 2, standard between-sex and between-condition contrast analyses showed that during mental rotation (as compared to the control condition),

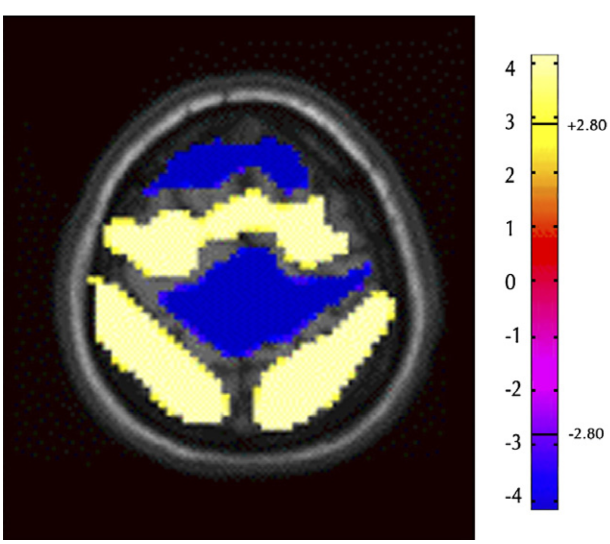

Fig. 2. Statistical parametric map of BOLD fMRI activity during mental rotation (as compared to the control condition) in 25 subjects (13 women), analyzed using standard between-condition contrasts. Note prominent frontal and parietal activation. Shown at $z = 60$ mm, voxel-wise $p < 0.005$.

both men and women activated bilateral prefrontal cortices, bilateral parietal (inferior and superior lobules), bilateral temporal–occipital regions and visual association cortices, in agreement with multiple prior mental rotation studies (e.g. [17,18]). See [11] for detailed results, including regions de-activated during mental rotation, which in general corresponded to a ''default'' brain network more active during rest than during most tasks [19,20].

3.3. Categorical analyses: Rotate (vs. Rest); Women vs. Men

As shown in Fig. 3a, between-sex comparisons during mental rotation revealed greater activity in women in bilateral dorsalmedial prefrontal cortex (DMPFC; $x = -9$, $y = 27$, $z = 51$; $x = 15$, $y = 30$, $z = 54$) – a region strongly implicated in top-down, effortful cognitive processing [21] including decision-making [22] and spatial working memory [23]. Greater frontal activity in women is in broad accord with the majority of prior functional neuroimaging studies of mental rotation demonstrating sex differences [3,6,24].

3.4. Univariate block-level ''seed'' connectivity analyses

As also reported in [11], in women, accurate mental rotation performance was significantly correlated inversely with brain activity in left (extending to right) middle frontal gyrus (MFG). In men, the only brain region significantly correlated with accurate performance was left posterior insula bordering on claustrum, with decreased activity associated with better performance. This posterior insula/claustrum region appears to correspond anatomically to the cortical projections of the vestibular system, referred to as parieto-insular vestibular cortex (PIVC) [25,26] and further discussed below and in [11]. The two brain regions found to be most associated with accurate performance in women and men (left MFG and left PIVC, respectively) were used as ''seed'' voxels in separate univariate functional connectivity analyses to identify brain networks differentially associated with accurate mental rotation performance in men and women. Brain regions identified as correlating positively with left MFG activity during mental rotation were similar for both men and women, and included bilateral frontal regions, bilateral angular gyri, bilateral temporal association cortices, and most prominently, bilateral posterior cingulate. In general, these regions appear to correspond to a ''default'' brain network previously shown to be active when subjects are not engaged in any particular task [19,20].

In contrast to similar MFG-correlated networks in men and women, PIVC-correlated networks differed markedly by sex. In men, left PIVC inversely-correlated activity was extensive, and consisted of a large-scale network of visuospatial-related brain regions including most prominently bilateral parieto-occipital association cortex (precuneus, BA 7), as well as right temporal–occipital regions, bilateral early/primary visual cortices, and bilateral posterior parahippocampal gyrus, extending on the left to the fusiform gyrus, as shown in Fig. 4. In women, inverse correlation with activity in left PIVC was relatively sparse. Automatic evocation by men to a greater extent than women of this visual/vestibular network during mental rotation may represent an effective, unconscious, ''bottom-up'' neural strategy which could reasonably account for men's traditional visuospatial performance advantage.

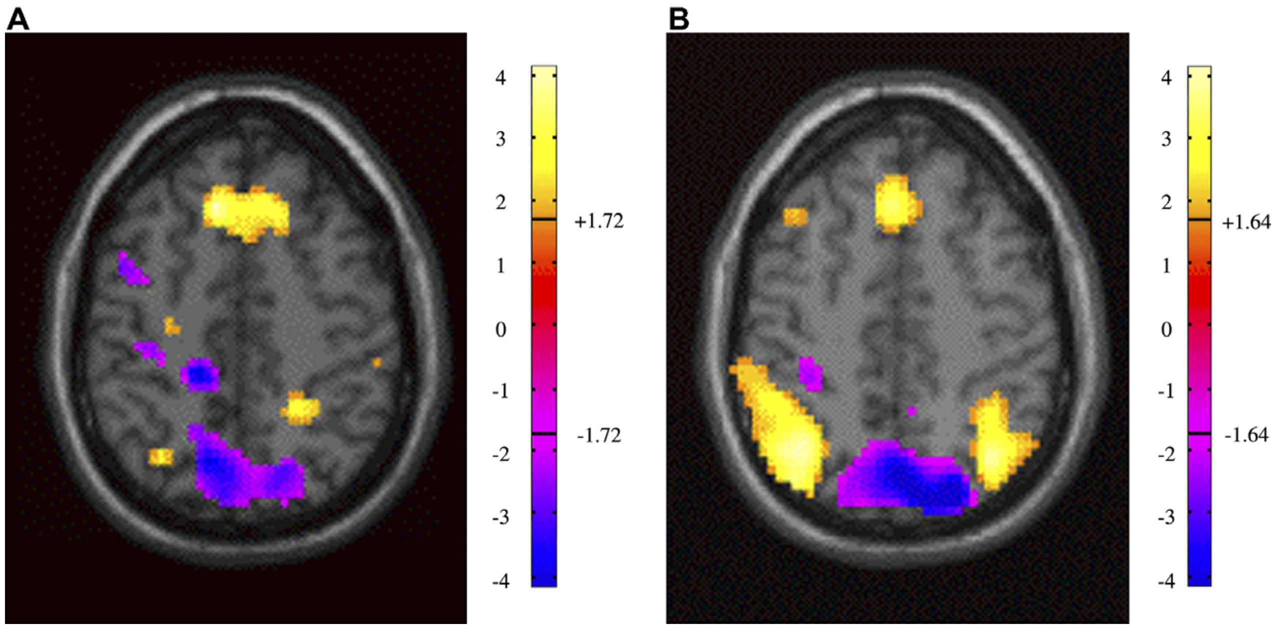

Fig. 3. Patterns of sex difference during mental rotation detected using between-group categorical analysis (A) and PCA (B). Categorical analysis compared Women vs. Men for the rotation vs. rest contrast. PCA was performed on the rotation vs. rest contrast with Principal Component 2 (PC2) correlating with sex. Both methods demonstrate greater dorsalmedial prefrontal cortex (DMPFC) activation in woman. However, PCA shows that activity in DMPFC is also associated with activity in bilateral parietal regions, and that this pattern of activity is more strongly expressed in women. Both maps show axial slice at $z = 48$ mm and are displayed at voxel-wise $p < 0.01$.

3.5. PCA using Rotation (vs. Rest) contrast images

Using Rotation contrast images (corresponding to brain areas activated during rotation as compared to rest, with one contrast image per subject), the first principal component (PC1) was found to account for 53.11% of total variance, indicating that the mental rotation activation task induced a robust, consistent patterns of brain activity. As shown in Fig. 5a, PC1 consisted of activation of bilateral middle frontal gyrus (BA 6), bilateral/midline superior frontal gyrus, bilateral inferior and superior parietal lobules and bilateral occipital and occipitotemporal regions, with de-activation in precuneus, bilateral rostral medial frontal gyri (BA 10), bilateral posterior insula (possibly corresponding to parieto-insular vestibular cortex; PIVC), and bilateral inferior parietal lobule (more posterior to the area of activation). This pattern of results matches closely those obtained by us, as shown in Fig. 2, using standard categorical analyses, and is in accord with multiple other studies of mental rotation [17,18]. PC1 can be considered the core mental rotation brain network.

3.6. PCA using Rotation vs. Control contrast images

When the Rotation vs. Control (0° rotation) contrast images were entered into PCA, PC1 turned out to be similar but not identical, as shown in Fig. 5b. The identified network still included bilateral prefrontal, frontal and parietal regions, but with much less occipital activation, as would be expected, since level of visual stimulation was designed to be identical between activation and control condition, and was therefore subtracted out by the contrast. More interestingly, PC1 using the contrast images included more prominent bilateral insula de-activation. Given that we consider this region to be a key node in a visual–vestibular network involved in the mental rotation process [11], that would not be expected to be involved during the control comparison condition, this finding indicates that subtracting out control activity may provide somewhat greater sensitivity for detecting specific parts of the network. However, entering between-condition contrast images into PCA must be done with caution, since the images upon which analysis is performed no longer correspond to the full set of brain regions active during a task, but to a subtraction image from which certain networks or parts of networks have been removed. It should also be noted that even entering a contrast image corresponding to the activation task versus resting constitutes a between-condition contrast insofar as the "resting state" is increasingly recognized to consist of a distinct pattern of activity corresponding to a default network [19,20]. Using an activation task to probe brain regions/circuits of interest serves as a filter through which brain networks specifically activated by the task (but not other aspects of the network) can be viewed.

3.7. PC1 correlation with education

PC1 correlated significantly with the level of education ($r = 0.43$, $p = 0.017$ for rotation; $r = 0.64$, $p = .0003$ for the rotation vs. control (0°) condition, but not with any other factors. What this means is that a subject's level of education (which ranged from 12 to 20 years) was associated with the degree to which he or she expressed the core mental-rotation-associated neural pattern. This finding will require replication using a prospective study design, but may relate to a subject's willingness and ability to follow instructions and comply with task demands – attributes likely associated with education. Level of aptitude for mental rotation, while also shown to be associated with aspects of education [27–29] is less likely to account for this finding, because PC1 did not correlate with either mental rotation performance ($r = 0.12$, $p > 0.2$) or perceived task difficulty ($r = 0.33$, $p > 0.05$). This finding is an example of PCA's ability to separate these factors and association.

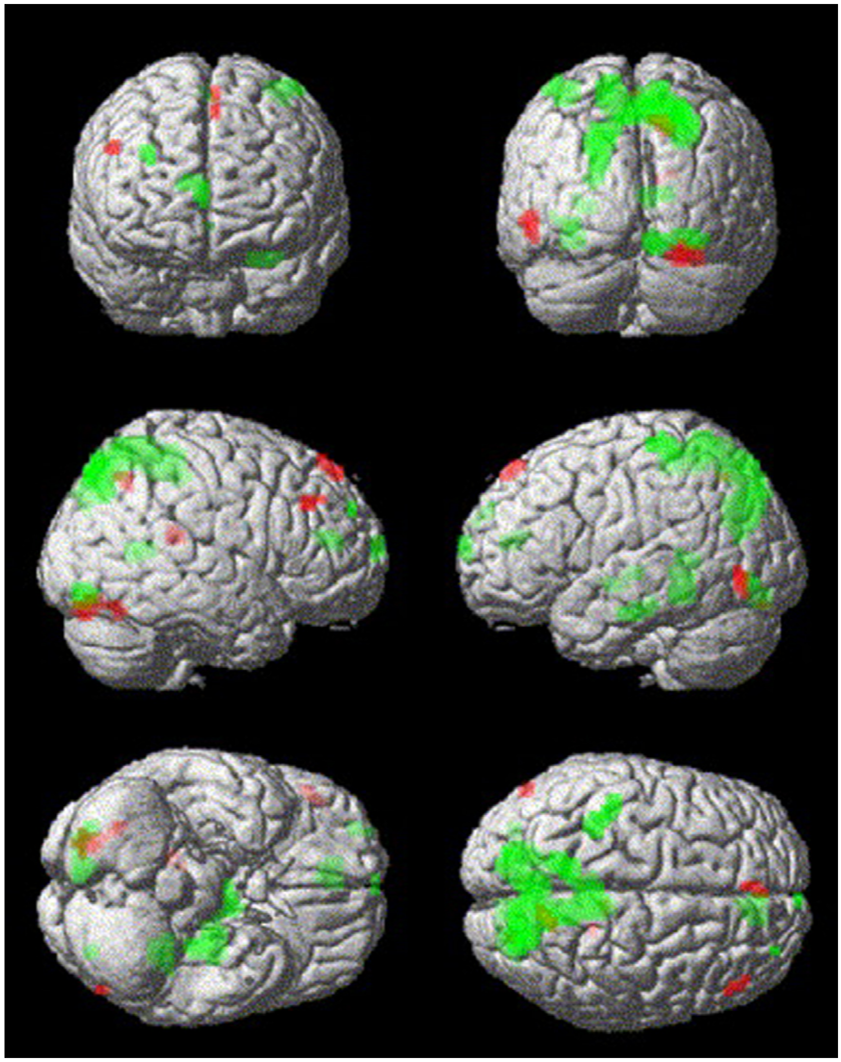

Fig. 4. Network of brain regions shown inverse correlation with activity in left parieto-insular vestibular cortex (PIVC; $x = -33$ mm, $y = -3$ mm, $z = 9$ mm) during mental rotation in men (green) and women (red). PIVC is the region mostly correlated with performance accuracy in men. Results are displayed at a threshold of $p < 0.05$, corrected for multiple comparisons over the whole brain. Note the extensive activation of parietal–occipital cortices in men, but not women. Mens' greater use of this visual–vestibular network during mental rotation may explain their traditional performance advantage for this task. This figure was taken from [11] and used with publisher's permission.

3.8. PC2 correlation with sex

PC2, accounting for 5.74% of total variance, was significantly differentiated according to sex ($r = 0.36$; $p = 0.039$). PC2 consisted of a pattern of activation (corresponding to greater activity in women) in bilateral/midline superior frontal gyrus/dorsalmedial prefrontal gyrus (DMPFG), bilateral right > left middle/inferior frontal gyri (dorsolateral prefrontal cortex, DLPFC), bilateral superior parietal lobule (BA 7), and left lateral occipital cortex, with de-activation (corresponding to greater activity in men) of posterior cingulate and bilateral postcentral gyri, as shown in Fig. 3b. These results, obtained in a data-driven fashion, match closely those obtained using an investigator-defined categorical approach of comparing directly men and women. In particular, greater DMPFC and left lateral occipital activation in women, and greater precuneus and postcentral gyri activation in men, were detected using both approaches. The similarity of results obtained using both methods are apparent in Fig. 3. These sex differences are broadly consistent with women taking a ''top-down'' approach to mental rotation, relying more upon high-order frontal regions such as DMPFC. Differences between the categorical and PCA approach include greater DLPFC activation detected using PCA. Given the role of DLPFC in effortful cognitive processing and working memory, it is likely that PCA was more sensitive in detecting reliance of women upon this region. PCA also revealed bilateral superior parietal activation, which has also been reported to be greater in women than in men [7], but was not significant using a categorical approach. The fact that PC2 – the sex-divergent pattern of activity – accounted for 5.74% of total variance, provides a framework for understanding the magnitude of neural sex differences during mental rotation.

3.9. PCA in men and women separately

While the above described PCA included both male and female subjects, and was therefore able to identify a sex-divergent pattern of activity in a data-driven manner, PCA was also examined in men and women separately. For both men and women, PC1 –

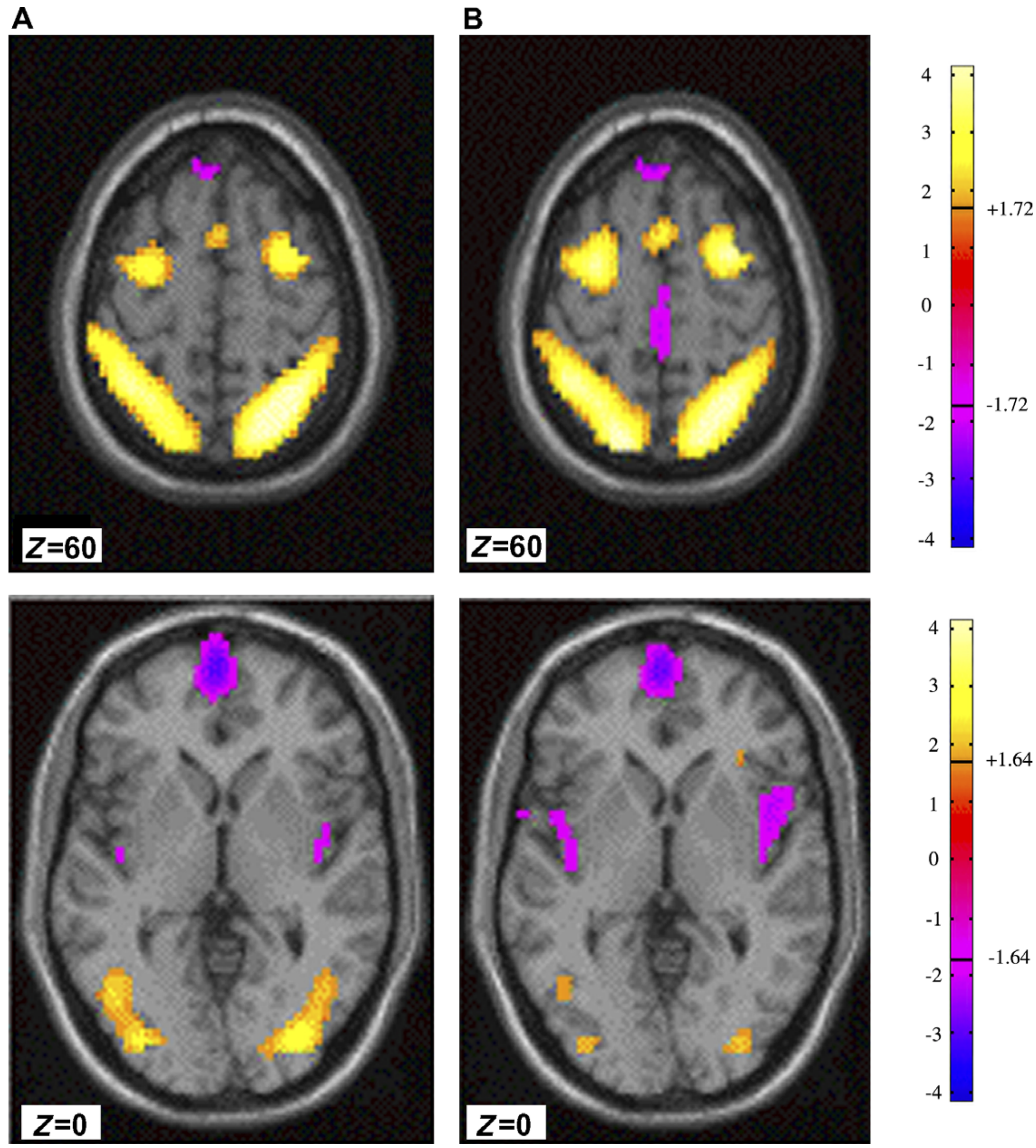

Fig. 5. Principal Component 1 (PC1) – the core mental rotation network – obtained using Rotation (vs. rest) contrast images (A) and Rotation vs. Control Condition contrast images (B). Both identified networks include bilateral prefrontal, frontal and parietal regions. Less occipital activation in the rotation vs. control contrast is expected, since level of visual stimulation was designed to be identical between both conditions, and was therefore subtracted out by the contrast. See text for discussion of other differences. Maps are displayed at both $z = 60$ mm and $z = 0$ mm and thresholded at $p < 0.01$, uncorrected.

which consisted predominantly of bilateral cortical activation – was very similar to PC1 identified on the mixed sex group (shown in Fig. 5), as would be expected since this principal component did not correlate with sex ($r = -0.0514$, $p = 0.6$). Interestingly, PC1 in men alone correlated with perceived task difficulty ($r = 0.62$, $p = 0.01$), while in women alone, PC1 correlated with education ($r = 0.62$, $p = 0.01$) as well as with performance accuracy (at a trend level, $r = 0.43$, $p = 0.07$). While speculative, it may be considered that these findings fit with the idea that men can perform mental rotation in a more automatic, less effortful manner, with less cortical activation and greater reliance upon subcortical structures known to be involved in skill and habit learning [30] Non-automatic, more effortful mental rotation performance might be associated with greater cortical activation, as demonstrated by the correlation of PC1 with task difficulty. Continued investigation and validation of these sex-specific brain networks involved in visuospatial processing can provide a method for assessing the contribution of factors such as sex hormones, psychosocial factors and genetics to network expression.

In sum, these different approaches to the analysis of an fMRI activation paradigm provide similar, complementary results. The data-driven PCA approach provides a helpful confirmatory function in this context. A key benefit of PCA is the ability to truly characterize interactions among brain regions during task performance, and to quantify patterns of covariance. These data-driven patterns can be correlated with other variables or measures post hoc. PCA may provide a foundation for future use in situations where group membership is not known, and can possibly be determined using these techniques. By quantifying, in a data-driven fashion, the contribution of factors such as sex and education to patterns of brain activity, our PCA 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 such as PCA can play in providing true network-based functional information, as well as quantifying the contribution of a given network's activity within and across different populations.

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