The relationship within and between the extrinsic and intrinsic systems indicated by resting state correlational patterns of sensory cortices

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Much Research has been done on extrinsic and intrinsic systems, which consist of brain regions associated with the processing of externally and internally oriented stimuli, respectively. However, understanding of the underlying relationships within and between these two systems is relatively limited. To improve our understanding of these underlying relationships, we investigated the positive and negative correlations of three regions of interest (ROIs) located in the auditory, visual and somatosensory systems by using resting state functional MRI (fMRI) with a large sample size. We found that all three sensory systems exhibited significant negative correlation with the intrinsic system. In contrast, positive correlations between these sensory cortices and brain regions outside their respective system were limited. The present study extended former findings by indicating that multiple subsystems rather than a single subsystem of the extrinsic system are inherently negatively correlated with the intrinsic system. In the present study, the brain regions associated with the processing of external inputs will be referred to as the “extrinsic system” to use the terminology of Golland et al. (2007). Accordingly, the auditory, visual and somatosensory systems as well as the “task-positive” network could be seen as subsystems of the extrinsic system.

Despite the fact that the majority of functional neuroimaging studies investigate externally oriented processes, several recent studies have begun to investigate internally oriented processes by using specially designed tasks (Kjaer et al., 2002; Lou et al., 2004; Decety and Sommerville, 2003). Interest in these internally oriented processes was sparked by the finding that a particular set of brain regions was deactivated during high-demanding cognitive task performances (Shulman et al., 1997; Gusnard and Raichle, 2001; Simpson et al., 2001; Mazoyer et al., 2001). This set of brain regions includes the posterior cingulate cortex (PCC)/precuneus, the medial prefrontal cortex (MedFC), the bilateral inferior parietal lobes (IPL), etc. These deactivations are believed to result from the interruption of the internally oriented processes by external stimuli (Shulman et al., 1997; for a review, see Gusnard and Raichle, 2001). Based on their PET study, Raichle et al. (2001) suggested that this set of brain regions may support a default mode of human brain function during the resting state, when the internally oriented processes are likely to occur. In the present study, those brain regions within the “default mode” network will frequently be referred to as the “intrinsic system” because of their association with internally oriented processing, in accordance with the terminology of Golland et al. (2007).

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Introduction

Functional neuroimaging techniques, such as positron emission tomography (PET) and functional MRI (fMRI), have been widely used to investigate the mechanisms of human brain functions such as perception and cognition. Typically a task is presented and the brain regions involved in the task can be obtained by evaluating the responses recorded by functional neuroimaging. An enormous amount of information has been accumulated about the systems specialized for externally oriented processes, such as perceptual processing (e.g., the auditory, visual and somatosensory systems) and exogenous cognitive processing (e.g., the “task-positive” network defined by Fox et al., 2005). In the present study, the brain regions associated with the processing of external inputs will be referred to as the “extrinsic system” to use the terminology of Golland et al. (2007). Accordingly, the auditory, visual and somatosensory systems as well as the “task-positive” network could be seen as subsystems of the extrinsic system.

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A few recent resting state fMRI studies reported intrinsic correlations within and between the extrinsic and intrinsic systems. Specifically, positive correlations of slow spontaneous fluctuations in the blood oxygen level dependent (BOLD) signals have been found within both the default mode network (Greicius et al., 2003; Fox et al., 2005; Fransson, 2005) and the subsystems of the extrinsic system, including the motor (Biswal et al., 1995; Lowe et al., 1998), visual (Cordes et al., 2000), auditory (Cordes et al., 2000), language (Hampson et al., 2002) and dorsal and ventral attention (Fox et al., 2006) systems. Greicius et al. (2003) first noticed the negative correlations of resting state spontaneous fluctuations. Fox et al. (2005) and Fransson (2005) expanded the findings by Greicius et al. (2003) by indicating that significant negative correlations of spontaneous fluctuations exist between the “task-positive” network, a subsystem of the extrinsic system, and the “task-negative” network, which was essentially the intrinsic system. These resting state functional network patterns have been found to be quite consistent across subjects (Beckmann et al., 2005; DeLuca et al., 2006; Damoiseaux et al., 2006; Fox et al., 2005) suggesting that the positive and negative correlations within and between systems may reflect the intrinsic human brain functional organization.

Previous findings relevant to the positive and negative correlations associated with the sensory systems, especially those relevant to the negative correlations, seem to be quite inconsistent. Fox et al. (2005) found neither the “task-positive” network nor the “task-negative” network was correlated with the sensory cortices during the resting state. The resting state study by Cordes et al. (2000) did not report significant negative correlations associated with the sensory cortices while analyzing their correlational patterns. The study by Greicius and Menon (2004) provided some clues for the existence of negative correlations between the sensory systems and the default mode network: the strength and size of the subjects’ activation to auditory and visual stimuli was found to be closely related to the extent of the default mode network being suppressed. In the study by Tian et al. (2007), the negative correlations associated with the sensory cortices were found to be unstable. In addition to the differences in the processing methods and the states used (e.g., resting state Fox et al., 2005; Tian et al., in press; and task performance Greicius and Menon, 2004), we suggest that the relatively small sample size adopted in these studies may also be a factor that introduced these inconsistencies since individual variations are expected to have a significant influence on the statistical results when the sample size is relatively small.

In the present study, we evaluated the positive and negative correlation of three representative sensory cortices, namely, the auditory, somatosensory and visual cortices using a large sample size to investigate whether the sensory systems are inherently correlated with other subsystems of the extrinsic system, and whether they are inherently negatively correlated with the intrinsic system. We chose to use a large sample size to diminish the influence of individual variations and thus to avoid any possible instabilities of the correlations of BOLD signals that could possibly occur when the sample size was comparatively small (Tian et al., in press). Indeed, the large sample size employed in the present study enabled us to gain new insights into the relationships within and between the extrinsic and intrinsic systems despite the resemblance in states (resting state) and methods (ROI-based correlation analyses) between Tian et al. (in press) and the present study.

Materials and methods

Subjects and imaging methods

Eighty-three normal subjects (37 females, 23.7 ± 3.8 years) participated in the present study after giving written informed consent in accordance with Xuanwu Hospital’s Review Board. All the subjects were recruited by advertisement. Due to excessive head motions, the functional images of 4 subjects were excluded from further analyses. All imaging was performed on a SIEMENS TRIO 3-T scanner at the Department of Radiology, Xuanwu Hospital. Each subject underwent a 9-min scan during a conscious resting state. Functional images were collected axially using an echo-planar imaging sequence sensitive to BOLD contrast. The acquisition parameters were 32 slices, 2000/30 ms (TR/TE), 3.0/1.0 mm (thickness/gap), 220 × 220 mm (FOV), 64 × 64 (resolution), 90° (flip angle). Other sessions not used in the present study will not be described here.

During the resting state scanning, the subjects were instructed to keep still with their eyes closed, as motionless as possible and not to think about anything in particular.

Data preprocessing

The first 10 volumes were discarded to reduce the influence of the scanner instabilities and to allow for subjects’ adaptation to the environment. The remaining functional scans were first corrected for within-scan acquisition time differences between slices and then realigned to the first volume to correct for within-run head motions. This realigning step provided a record of head motions within each fMRI run. Subsequently, the functional scans were spatially normalized to a standard template (Montreal Neurological Institute) and resampled to 3 × 3 × 3 mm³. All these processes were conducted using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). Three possible sources of artifacts were then removed from the data through linear regression (Fox et al., 2005; Salvador et al., 2005; Golland et al., 2007). These were (1) 6 head motion parameters obtained in the realigning step, (2) the whole brain signal obtained by averaging the time series of all the voxels within the brain and (3) the linear trend. Finally, the waveform of each voxel was temporally band-pass filtered (0.01–0.08 Hz) using AFNI (http://afni.nimh.nih.gov/) to reduce the influences of low-frequency drift and high-frequency noise.

Since correlational analysis is sensitive to head motions, the data sets with the maximum displacement in any cardinal direction (x, y, z) greater than 1 mm were discarded. As mentioned above, images of only 79 subjects were available for later analyses.

Correlational analysis

In the present study, we examined the positive and negative correlations of the auditory, somatosensory and visual cortices using an ROI-based method. ROIs for the auditory, somatosensory and visual cortices were defined as the 6-mm-radius spheres centered in the left AI (Talairach coordinates [−56, −17, 6]), left SI (Talairach coordinates [−47, −31, 55]) and left VII (Talairach coordinates [−27, −84, −2]), respectively. The centres for the auditory and visual ROIs were decided according to the activation peaks in a previous study (Tian et al., in press), and the one for the somatosensory ROI was decided according to the peak identified in
another study (Blankenburg et al., 2003). Illustrations of the location of the ROIs can be found in Fig. S1 in the supplementary materials on the NeuroImage Web site.

Seed reference time courses were obtained by averaging the time series of all voxels in the ROIs. To obtain subject-specific correlation maps for each ROI, Pearson’s correlation analysis was performed between the specific seed reference time course and time series from the whole brain on a voxel-wise basis. This produced spatial maps in which the values of the voxels represented the strength of the correlation with the ROIs. Finally, the correlation coefficients were transformed into z-scores using Fisher’s transformation to improve normality (Press et al., 1992).

**Statistical analysis**

A random-effect (Holmes and Friston, 1998) one-sample t-test was performed to obtain within-group positive and negative correlation maps. The random-effect analysis estimates the error variance across subjects, rather than across scans, and thus allows the present results to be generalized to normal populations. A large sample size will allow a stringent threshold for the following two reasons: (1) It enhances the t-score (\( t = \frac{\bar{x} - \mu_0}{S/\sqrt{n}} \); \( t \) will increase when the sample size \( n \) is increased). (2) It enhances the degrees of freedom and thus a lower p-value can be obtained for the same t-score. In the present study, the large sample size enabled us to choose a threshold of \( P < 0.00001 \) (FWE corrected) and cluster size >2700 mm\(^3\) (100 resampled voxels). Statistical maps were produced by superimposing the statistical results onto a glass brain as well as rendering these results onto a 3D brain reconstruction provided by SPM2 (http://www.fil.ion.ucl.ac.uk/spm/).

**Results**

**Positive correlations**

Each ROI was strongly coupled with its contralateral counterpart (Table 1, Fig. 1d). In addition, positive correlations between these sensory cortices and brain regions outside their respective system were relatively limited in extent. Specifically, the left VII had no positive correlation with brain regions outside the visual system. The left AI was also positively correlated with the supplementary motor area (SMA, BA6) (Figs. 1a–b, Table 1), a component of the “task-positive” network, while the clusters within the bilateral auditory cortices (60048 mm\(^3\)) were 13.5 times larger than that in the SMA (4131 mm\(^3\)). The left SI was also positively correlated with two frontal regions (Figs. 1c–d, Table 1), while the cluster size in the bilateral somatosensory cortices (60750 mm\(^3\)) was 10.0 times that in the frontal lobe (6048 mm\(^3\)). It should be noted that when the threshold was lowered, more positive correlations between these sensory cortices and brain regions outside their respective system would occur (please refer to Fig. S2 in the supplementary materials on the NeuroImage Web site to find the positive correlation maps thresholded at \( P < 0.05 \) (FWE corrected) and cluster size >2700 mm\(^3\)).

**Negative correlations**

All three negative correlation maps shared some resemblance to the default mode network (Fig. 2, Table 2). Specifically, the left VII was negatively correlated with all three representative components of the default mode network, the PCC/precuneus, the MedFC and the bilateral IPL (Figs. 2e–f, Table 2). In addition to these four brain regions, the bilateral superior frontal gyrus in symmetric positions was also negatively correlated with the left VII (Figs. 2e–f). Besides the three representative components of the default mode network, the left SI was also negatively correlated with symmetric areas of the bilateral cerebellum (Figs. 2c–d, Table 2). The left AI showed significant negative correlation only with two of the three representative components of the default mode network, the PCC/precuneus and the left IPL (Figs. 2a–b, Table 2). In addition, when the threshold was lowered, a more complete default mode network appeared in the negative correlation maps (please refer to Fig. S3 in the supplementary materials on the NeuroImage Web site to find the negative correlation maps thresholded at \( P < 0.05 \) (FWE corrected) and cluster size >2700 mm\(^3\)), and more obvious similarities between these negative correlation maps also occurred (please refer to Fig. S4 in the supplementary materials on the NeuroImage Web site to find the overlap maps of the three negative correlation maps).

**Discussion**

To investigate whether the sensory systems are inherently correlated with other subsystems of the extrinsic system, and whether they are inherently negatively correlated with the intrinsic system, we evaluated the positive and negative correlations of three sensory cortices with a large sample size using resting state fMRI. A large sample size enabled us to largely diminish the influences of individual variations that may have significant influence on statistical results when the sample size is relatively small (Tian et al., in press).

Moreover, as has been mentioned, a large sample size can enhance the t-score as well as the degrees of freedom and ultimately lead to a stringent threshold. In the present study, the large sample size enabled us to employ a threshold of \( P < 0.00001 \) (FWE corrected) and cluster size >2700 mm\(^3\). Under this threshold, the clusters within the correlation maps were neither too widespread nor too limited. More importantly, the positive correlation maps obtained under this threshold were consistent not only with those obtained using ROI-based correlational analysis (Cordes et al., 2000; Tian et al., in press), but also with those obtained using probabilistic independent component analysis (Beckmann et al., 2005; Damoiseaux et al., 2006).

A number of correlations between the subsystems of the extrinsic system could only survive a lowered threshold (Fig. S2).
In other words, compared to the correlations within subsystems as well as those between the extrinsic and intrinsic systems, those between the subsystems of the extrinsic system seem to be limited in extent, at least, when using the present stringent threshold. Specifically, the visual system was not positively correlated with any other subsystems of the extrinsic system (Figs. 1e–f, Table 1).

In the auditory correlation map (Figs. 1a–b, Table 1), the size of clusters within the auditory cortices occupied a relatively large percent of the volume of the auditory system, while the cluster size of the SMA occupied a quite small percent of the overall volume of other subsystems of the extrinsic system. Similarly, in the somatosensory correlation map (Figs. 1c–d, Table 1), the size of clusters within the frontal regions also occupied a quite small percent of the overall volume of other subsystems of the extrinsic system. Considering the enormous functional interactions within subsystems as well as those between the extrinsic and intrinsic systems, as reflected by their extensive correlations, we suggest that the interactions between the subsystems of the extrinsic system seem to be relatively limited.

All three sensory systems were negatively correlated with the default mode network (Fig. 2, Fig. S3, Fig. S4, Table 2). Among these three systems, the bilateral SII were the only brain regions that have been reported to be intrinsically anti-correlated with the default mode network (Fransson, 2005). However, the study by Greicius and Menon (2004), although carried out during task performance, indirectly provided evidence of the intrinsic anti-correlations between the default mode network and the auditory and visual systems. In their study, the extent of the default mode activity being suppressed was found to be positively correlated with the height and extent of the activation of the auditory and visual cortices (Greicius and Menon, 2004).

As has been mentioned, Fox et al. (2005) and Fransson (2005) found only significant negative correlations between the “task-positive” network and the default mode network. The present study extended the previous findings (Greicius et al., 2003; Fox et al., 2005; Fransson, 2005) by indicating that multiple subsystems, rather than a single subsystem, of the extrinsic system are negatively correlated with the intrinsic system. In accordance with
the suggestion that negative correlations may play a differentiating or competing role (Fox et al., 2005), we suggest that these widespread negative correlations between the extrinsic and intrinsic systems may facilitate the functional competition, or at least differentiation, between these two systems. This suggestion is consistent with our daily experience in which externally and internally oriented processes can always disturb or even interrupt each other. Specifically, external stimuli can often diminish internally oriented processes that have been suggested to be the role of the default mode network, such as general information gathering and evaluation (Raichle et al., 2001; Gusnard and Raichle, 2001), task-independent thought (Binder et al., 1999; McKiernan et al., 2006), episodic memory (Greicius et al., 2003) and self-referential processing (Northoff and Bermpohl, 2004). Similarly, internally oriented processes can also disturb externally oriented processes (Teasdale et al., 1995; Giambra, 1995; McKiernan et al., 2003).

Considering the intrinsic negative correlations between the sensory systems and the default mode network, one might expect that sensory task performance would lead to the default mode network deactivation. However, to our knowledge, no previous study reported default mode deactivations during sensory task performance. This inconsistency can be explained by the study by Greicius and Menon (2004). In their study, both the strength and size of the activations in the auditory and visual cortices were found to increase with the suppression of the default mode activity, while little to no deactivation was found in the default mode network. Based on their findings, Greicius and Menon (2004) concluded that “not all tasks are sufficiently engaging to disrupt the default mode network”, that is, such factors as task difficulty and task novelty can also influence default mode network deactivation.

Two important issues with respect to the present finding of significant negative correlations between the sensory systems and the default mode network still need to be addressed. One issue is that the present finding of significant negative correlations between the sensory systems and the default mode network seems to be inconsistent with a few previous resting state fMRI studies. First,
The extrinsic systems were not found to be correlated with each other at the current stringent threshold, though they each exhibited significant negative correlation with the default mode network.

Overall, by evaluating the correlation patterns of three sensory ROIs based on a large sample size, we found that positive correlations associated with each sensory system were relatively limited in extent, while each sensory system exhibited significant negative correlations with the default mode network. The present study extended former findings (Greicius et al., 2003; Fox et al., 2005; Fransson, 2005) by indicating that multiple subsystems, rather than a single subsystem, of the extrinsic system are inherently anticorrelated with the intrinsic system. We suggest that these negative correlations between the extrinsic and intrinsic systems may reflect the inherent functional competition or differentiation between them. In addition, we suggest that the functional interactions between the subsystems of the extrinsic system are relatively limited compared to those within subsystems as well as those between the extrinsic and intrinsic systems.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2007.03.044.

References


Table 2

<table>
<thead>
<tr>
<th>ROI</th>
<th>Region</th>
<th>Cluster size, mm³</th>
<th>BA (peak)</th>
<th>Talairach (peak)</th>
<th>t-score (peak)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Af</td>
<td>B PCC/precuneus</td>
<td>12,852</td>
<td>23/7</td>
<td>0–56 39</td>
<td>11.93</td>
</tr>
<tr>
<td></td>
<td>L IPL</td>
<td>3807</td>
<td>39</td>
<td>−45 –68 39</td>
<td>9.45</td>
</tr>
<tr>
<td>Left SI</td>
<td>B PCC/precuneus</td>
<td>22,950</td>
<td>23/31/7</td>
<td>−9 –48 33</td>
<td>13.89</td>
</tr>
<tr>
<td></td>
<td>B MedFC/ACC</td>
<td>26,703</td>
<td>8/10/0</td>
<td>0 56 19</td>
<td>13.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11/32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L IPL</td>
<td>6372</td>
<td>39/40</td>
<td>−45 –57 33</td>
<td>11.31</td>
</tr>
<tr>
<td></td>
<td>R IPL</td>
<td>3969</td>
<td>39/40</td>
<td>56 –60 33</td>
<td>10.27</td>
</tr>
<tr>
<td></td>
<td>R Cerebellum</td>
<td>5346</td>
<td></td>
<td>30 –86 –23</td>
<td>15.76</td>
</tr>
<tr>
<td></td>
<td>L Cerebellum</td>
<td>5346</td>
<td></td>
<td>−24 –86 –23</td>
<td>12.98</td>
</tr>
<tr>
<td>Left VII</td>
<td>L IPL</td>
<td>13,014</td>
<td>39/40</td>
<td>−59 –51 36</td>
<td>14.38</td>
</tr>
<tr>
<td></td>
<td>R IPL</td>
<td>13,068</td>
<td>39/40</td>
<td>45 –68 45</td>
<td>13.90</td>
</tr>
<tr>
<td></td>
<td>L SFG</td>
<td>4293</td>
<td>8</td>
<td>−24 23 51</td>
<td>10.77</td>
</tr>
<tr>
<td></td>
<td>B MedFC</td>
<td>5778</td>
<td>8/9</td>
<td>−3 45 31</td>
<td>10.42</td>
</tr>
<tr>
<td></td>
<td>R SFG</td>
<td>5535</td>
<td></td>
<td>36 17 52</td>
<td>10.42</td>
</tr>
<tr>
<td></td>
<td>B PCC</td>
<td>3051</td>
<td>23</td>
<td>0 –39 41</td>
<td>9.32</td>
</tr>
</tbody>
</table>

Height threshold was P<0.00001 (FEW corrected); extent threshold was cluster size >2700 mm². Abbreviations: L—left, R—right, B—bilateral, BA—Brodmann’s area, PCC—posterior cingulate cortex, IPL—inferior parietal lobe, ACC—anterior cingulate cortex, MedFC—medial frontal cortex, SFG—superior frontal gyrus.

former resting state fMRI studies using the same sensory cortices as ROIs as we used did not report significant negative correlations associated with them (Cordes et al., 2000, 2001). We suggest that this may have primarily been caused by the fact that whole brain signals, which were not removed in the studies by Cordes et al. (2000, 2001), can enhance the correlations throughout the entire brain (Laurienti, 2004). Secondly, in our former study (Tian et al., in press), no consistent negative correlations were observed between auditory, visual systems and the default mode network. We suggest that this could have resulted from individual variations within these negative correlations. In the present study we used a large sample size to decrease the influence of individual variations and thus obtained significant negative correlations. Thirdly, in the study by Fox et al. (2005), the default mode network was found to have no significant correlation with any sensory system. We suggest that this may have been caused by individual variations in these negative correlations, since the fixed-effect analysis method used in the study would be sensitive to individual variations (Holmes and Friston, 1998). Moreover, the specific choice of ROI-centres may also influence the ultimate negative correlational patterns.

The second issue that needs to be addressed is why the subsystems of the extrinsic system exhibited limited positive correlation with each other, considering our finding that they each negatively correlated with the default mode network. Numerous functional connectivity analyses have demonstrated that the correlational relationship was not a transferable one (e.g., Greicius et al., 2003). This means that significant correlation between brain regions “A” and “B”, as well as between “B” and “C” does not necessarily lead to significant correlation between brain regions “A” and “C”. It is certainly possible that correlation between brain regions “A” and “C” might survive a lowered threshold considering that they both significantly correlated with brain region “B”. Applying the above rule, that they are not necessarily correlated, it would be reasonable to expect that the subsystems of the extrinsic system were not found to be correlated with each other at the current stringent threshold, though they each exhibited significant negative correlation with the default mode network.