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Extrinsic and Intrinsic Systems in the Posterior Cortex of the Human Brain Revealed during Natural Sensory Stimulation

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When exposing subjects to a continuous segment of an audiovisual movie, a large expanse of human cortex, especially in the posterior half of the cerebral cortex, shows stimulus-driven activity. However, embedded within this widespread activity, there are cortical regions whose activity is dissociated from the external stimulation. These regions are intercorrelated among themselves, forming a functional network, which largely overlaps with cortical areas previously shown to be deactivated by task-oriented paradigms. Moreover, the network of areas whose neuronal dynamics are associated with external inputs and the network of areas that appears to be intrinsically driven complement each other, providing coverage of most of the posterior cortex. Thus, we propose that naturalistic stimuli reveal a fundamental neuroanatomical partition of the human posterior cortex into 2 global networks: an "extrinsic" system, comprising areas associated with the processing of external inputs, and an "intrinsic" system, largely overlapping with the task-negative, default-mode network, comprising areas associated with—as yet not fully understood—intrinsically oriented functions.

Keywords: default mode, fMRI, global network, intrinsic, natural viewing

Introduction

Functional mapping of the human cerebral cortex has been an active and highly productive domain of research in cognitive neuroscience. Functional imaging aimed at unveiling functional subdivisions of the cortex adds a powerful new perspective to previous mapping techniques because it allows a large-scale view of the cerebral cortex in its entirety (Raichle 1998, 2003; Van Essen and others 1998). Besides providing important information regarding the location of different functional areas, the search for cortical subdivisions has been motivated by the notion that understanding cortical neuroanatomical organization provides important insights into the functional specialization of the brain (Malach and others 2002).

On the largest scale, the human cortex was traditionally divided between prefrontal regions devoted to complex cognitive functions, such as planning, and executive activity and posterior regions, associated with various aspects of sensory processing. In particular, the functional topography of the posterior cortex has been extensively studied, and detailed cortical subdivisions were discovered. Functional mapping studies focused primarily on identifying the details of domain-specific cortical areas; however, larger organizational principles have also been proposed (Ungerleider and Mishkin 1982; Van Essen and Maunsell 1983; Levy and others 2001; Grill-Spector and Malach 2004). In the present study, we use natural stimuli to examine such large-scale organization in the posterior half of the cortex.

We used natural viewing of perceptually rich audiovisual stimulation in an attempt to disentangle regions engaged in processing incoming information and regions whose activity is dissociated from the external input. In a recent study, Hasson and others (2004) used natural viewing of audiovisual movies demonstrating that the time course of activity in a large expanse of the posterior cortex shows a remarkable level of voxel-by-voxel intersubject correlation when subjects are presented with the same movie sections. The similarity of activity across different brains manifested robust, time-locked responses to external stimuli in a diverse network of areas. Furthermore, in contrast to strictly controlled stimuli that are usually necessary to investigate narrowly tuned neuronal selectivity, this natural and perceptually rich sensory input activated a large expanse of regions of diverse functionality (Bartels and Zeki 2004; Hasson and others 2004).

However, embedded within this correlated territory, there were several anatomical "islands" that consistently failed to show intersubject correlations. Here we show that these islands form an internally linked system whose activity is dissociated from external processing and thus suggest a neuronal substrate for internally originated cognitive processes.

The functional distinction between internal and external processing has long been acknowledged by psychologists suggesting that in addition to external information processing, there exists an internally generated activity in the human mind (James 1890; Antrobus 1968; Singer 1975; Pope and Singer 1978; Binder and others 1999). Several studies explicitly explored the alternating interplay between the exogenous (external) and endogenous (internal) sources of processing, as well as factors affecting it (Antrobus and others 1966; Pope and Singer 1976; Giambra 1995; Teasdale and others 1995). The externally driven processing has been widely investigated in the cognitive neuroscience research, and a variety of sensory regions, largely confined to the posterior cortex, have been discovered. Internally driven processing is more difficult to explore experimentally due to its spontaneous nature. However, recent studies began to unravel the neural substrate of such processes, using tasks that were specifically designed to elicit internal thought processes (e.g., Kjaer and others 2002; Decety and Sommerville 2003; Gallagher and Frith 2003; Lou and others 2004).

The internal activity is associated with a resting state, which is commonly used as a baseline condition in sensory processing research. A number of studies have recently demonstrated a network of cortical areas associated with enhanced activity during resting state (Gusnard and Raichle 2001; Raichle and others 2001). These regions, which were termed the "default-mode" regions, were shown to undergo deactivations during a variety of cognitive tasks (Shulman and others 1997; Mazoyer and others 2001; McKiernan and others 2003) and are believed to reflect internally driven functions, which are interrupted during externally driven performance (Binder and others 1999; Gusnard and Raichle 2001).

Our study confirms and extends this set of findings by demonstrating the emergence of a 2-network system during processing of natural stimuli by the human brain: an "extrinsic" system, which is engaged by processing various aspects of the incoming information, and an "intrinsic" system, which is dissociated from such processing. (Some of these results were presented previously in an abstract form; Golland and others 2005).

Materials and Methods

Subjects

Twelve healthy subjects participated in one or more of the functional magnetic resonance imaging (fMRI) experiments. All subjects participating in the fMRI experiments had normal or corrected to normal vision and provided written informed consent to participate in the experiments. The Tel-Aviv Sourasky Medical Center approved the experimental protocols.

Stimuli and Experimental Design

Stimuli were generated on a PC, projected via an LCD projector (Epson MP 7200) onto a tangent screen positioned over the subject's forehead, and viewed through a tilted mirror.

Repeated Movie Experiment

Eight subjects participated in the repeated movie experiment. The experiment was 16min9s long and contained an uninterrupted segment of the classical western "The Good, the Bad, and the Ugly" directed by Sergio Leone. The experiment started with a 30-s blank screen followed by 9 s of geometrical patterned stimuli, which, in addition to the final 30 s of the functional data, were excluded from the analysis, to eliminate possible onset and offset effects. Each subject was exposed to the same movie segment in 2 different sessions.

Additionally, 5 of the above subjects were presented with another, different segment of the movie of an identical length. The results for this segment were used for comparison in the nonparametric testing procedure described below.

For the audio control experiment, 2 of the above subjects were presented with the original movie segment, without the sound track.

Rest Experiment

Five of the subjects who participated in the movie experiment also participated in the rest experiment. Subjects' eyes were closed throughout the experiment. They were instructed to pay close attention to any visual-like percept that might occur during the scan (e.g., visual-like dots) and to report it following the scan. The experiment was 615 s long.

Visual Localizer Experiment

Twelve subjects participated in the visual localizer experiment. An interleaved short block design was used in the experiment. Each epoch lasted 9 s, followed by a 6-s blank screen. The visual stimuli used included line drawings of faces, buildings, common man-made objects, and geometric patterns presented while the subjects performed a "one-back" task. During the experiment, 1 or 2 consecutive repetitions of the same image occurred in each epoch. The experiment lasted 450 s. For detailed description, see Hasson and others (2003).

Data Acquisition

Subjects were scanned in a 1.5-T Signa Horizon LX 8.25 General Electrics scanner equipped with a standard head coil. Blood oxygenation level–dependent (BOLD) contrast was obtained with gradient-echo echo-planar imaging sequence (time repetition = 3000, echo time = 55, flip angle = 90, field of view 24 × 24 cm^2, matrix size 80 × 80). The scanned volume included 24–27 nearly axial slices of 4-mm thickness and 1-mm gap, covering the whole cortical surface. T_1-weighted high-resolution (1 × 1 × 1 mm) anatomical images and 3-dimensional (3D) spoiled gradient-echo sequence were acquired on each subject.

Data Analysis

General

The fMRI data were analyzed using the "BrainVoyager" software package (R. Goebel, Brain Innovation, Masstricht, The Netherlands) and in-house software. The detailed procedures for 3D reconstruction and creation of the flattened cortices were published elsewhere (Levy and others 2001). Preprocessing of functional scans included 3D motion correction, linear trend removal, and slice scan time correction. To minimize the effect of global drift, a whole-brain average signal was removed from the repeated movie experiment data through linear regression. For the functional connectivity analysis, the same procedure was performed on the rest and localizer data. Filtering out of low frequencies of up to 10 cycles per experiment was applied to the repeated movie experiment, of up to 6 cycles to the rest experiment, and of up to 4 cycles to the visual localizer experiment. The data were spatially smoothed with a Gaussian filter of full width of half maximum value of 8 mm.

Significance levels of the statistical maps in Figures 1, 2, and 3 were corrected for multiple comparisons using false discovery rate (FDR) control (e.g., Benjamini and Yekutieli 2001). The FDR was controlled over the cortical surface voxels (not including white matter and subnuclei).

Mapping Intrasubject Correlation

We used the Pearson correlation coefficient $r^i_{x,y}(v)$ as a statistic that measures similarity between the 2 time courses x_t and y_t for subject i at voxel v. To create maps of statistical significance of the intrasubject correlation, we used $r^i_{x,y}(v)$ to test the null hypotheses that for this subject there is no correlation between the time courses at the voxels (H_o: $\rho^i_{x,y}(v)=0$). It was previously established that the observed BOLD signal can be partitioned into components of interest, confounds, and errors (Friston 1995). To accommodate complex effects of the confounding factors such as scanner noise, stimulus-independent hemodynamic effects, and spatial and serial correlation patterns, we chose to estimate the distribution of $r^i_{x,y}(v)$ under the null hypothesis nonparametrically, while preserving the confounding structure and the structure of errors. This distribution was estimated empirically, by calculating control voxel-by-voxel intrasubject correlation $r^i_o(v)=r^i_{x,z}(v)$ between the original movie segment x_t and an additional, different movie segment z_t, therefore leading to an expected mean $\rho_{xz} = 0$ (performed for 5 subjects for whom we had additional movie segment data). Because besides the content of the movie, all other scanning parameters were identical in the experimental and control conditions, we assume that the estimated control distribution can serve well as the null distribution for testing the correlation at the experimental condition. The observed null distributions were close to normal with slight differences at the ends of the statistic range (see Supplementary Fig. 3 for the standard normal Quantile-Quantile plot of the 5 subjects). The means and standard deviations (SDs) of the correlations over each subject under the null distributions were 0.01 ± 0.08, –0.006 ± 0.07, –0.009 ± 0.08, 0.01 ± 0.07, and 0.02 ± 0.08. Supplementary Figure 3*B* illustrates the difference between the control distribution of $r^i_0(v)$ and the experimental distribution of $r^i_{x,y}(v)$, both empirically estimated from a single subject's cortical data. Clearly, the experimental distribution is both shifted and skewed to the right relatively to the control distribution. For the remaining 2 subjects who did not participate in the additional movie screening, we pooled the distributions of the subjects together to construct average null distribution (0.006 ± 0.08).

The calculation was limited to the cortical voxels only (N ~30 000). The voxel-level P values of the intrasubject correlation coefficients in the repeated session paradigm were directly estimated from the smoothed (cubic smoothing spline) cumulative null distribution. For estimating the P value for the values outside the range of the empirical null distribution, the inverse of the number of data points available for estimating the control distribution was used as a conservative estimate. Finally, statistical maps were corrected for multiple comparisons through an adaptive, 2-stage FDR procedure at level $q = 0.05$ (Benjamini, Krieger, and Yekutieli 2005b). This procedure uses the original FDR procedure once to get an estimate of the number of true hypotheses and uses it again at a modified higher level. The procedure is known to control the FDR even for highly dependent test statistics (for its

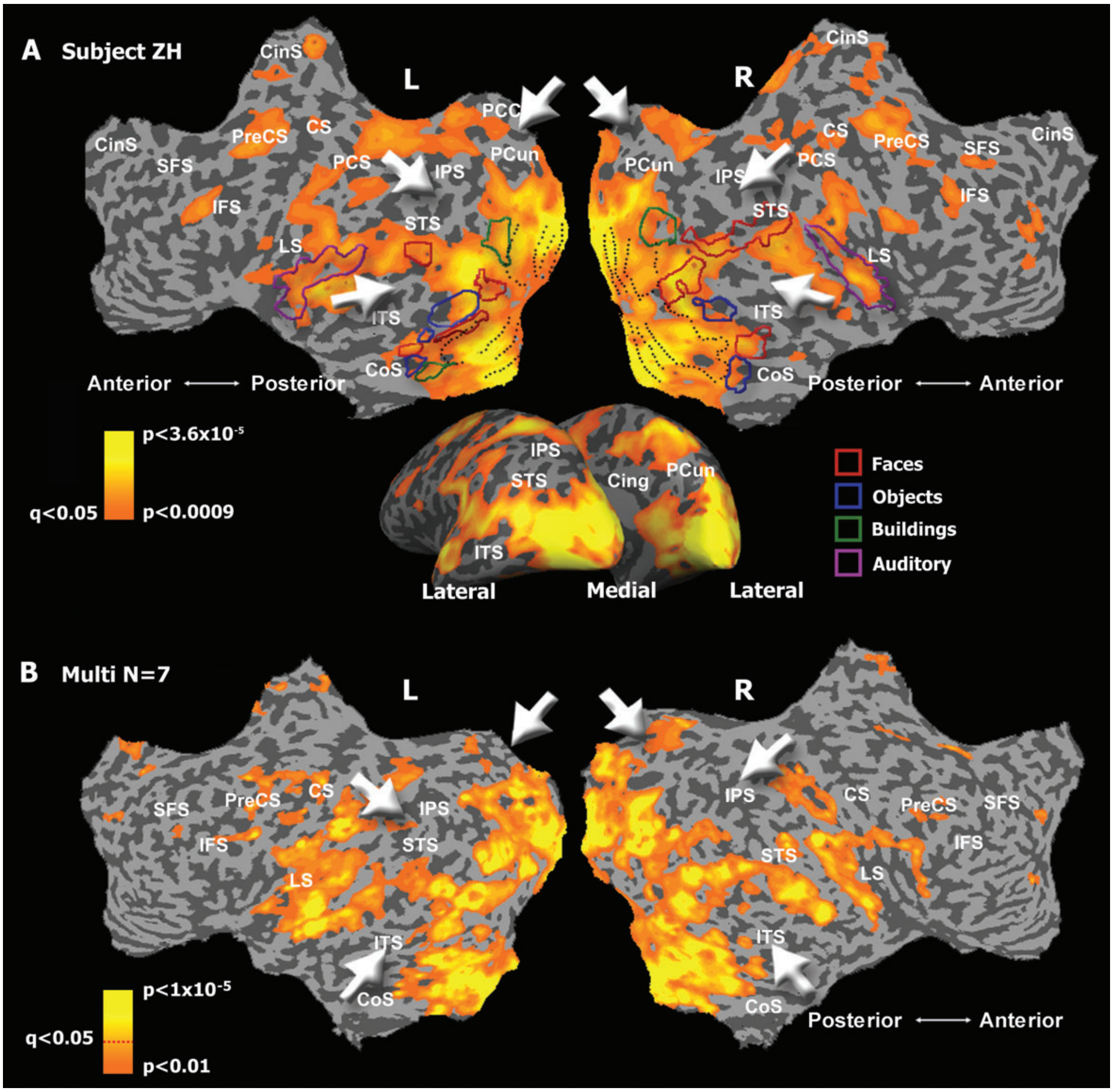

Figure 1. Neuroanatomical organization of movie-related activity. (*A*) Single-subject analysis. Neuroanatomical distribution of voxel-by-voxel intrasubject correlation of activity during repeated movie presentation. Correlation maps are presented on unfolded (top) and inflated (bottom) left (L) and right (R) hemispheres. The color indicates correlation coefficient of each voxel's activity across 2 movie presentations ($0.2 < r < 0.7$, $q(\mathrm{FDR}) < 0.05$). White arrows indicate areas in the posterior cortex that showed low levels of correlation. The borders of auditory cortex as well as different category-related visual areas are also delineated. Note that these sensory regions exhibit a high level of intrasubject correlation. (*B*) Group analysis. Neuroanatomical distribution of intrasubject correlation as revealed by multi-subject ($N = 7$) groupwise *t*-test analysis ($P < 0.01$, $q(\mathrm{FDR}) < 0.15$, the significance level of $q(\mathrm{FDR}) < 0.05$ is marked on the color bar). The color indicates *t*-value significance. CoS, collateral sulcus; ITS, inferior temporal sulcus; STS, superior temporal sulcus; IPS, inferior parietal sulcus; LS, lateral sulcus; PCun, precuneus; CS, central sulcus; PreCS, precentral sulcus; PCS, postcentral sulcus; CinS, cingulate sulcus; IFS, inferior frontal sulcus; SFS, superior frontal sulcus.

properties in the context of fMRI analysis, see Heller and others 2006). The mean significance cutoff correlation coefficient of this analysis was $r_c = 0.21$. The range of intrasubject correlation coefficients $r^i_{x,y}$ depicted in Figure 3*A* by orange color is ZH: $0.2 < r < 0.7$; NT: $0.24 < r < 0.64$; EQ: $0.22 < r < 0.71$; SO: $0.22 < r < 0.65$; SN: $0.2 < r < 0.67$; FM: $0.21 < r < 0.52$; SZ: $0.22 < r < 0.74$.

One subject showed deviant results, exhibiting high levels of intrasubject correlation in inferior parietal cortex (IPC) and posterior cingulate cortex/precuneus (PCC/PCun) regions. Because this pattern was different from the other 7 subjects and because the functional connectivity analysis is based on the existence of uncorrelated foci in the region of IPC, this subject was excluded from further analysis.

For the group-level analysis, we calculated the average correlation of $r^i_{x,y}(v)$ across subjects $i = 1, 2, \ldots, k$ (Figs 1*B* and 3*B*). As noted above, raw correlations had close to normal distribution in all subjects, more than the Fisher-transformed correlations. All further analyses were therefore performed on the raw correlations. Relying on the approximate normality of $r^i_{x,y}(v)$, we may then test the group-level hypothesis that $\rho_{x,y}(v)=0$ using *t*-tests. To further examine the validity of the assumption, we used again $r^i_0(v)$ to construct an empirical control distribution, but this time at the group level, calculating from them groupwise *t*-statistic at each voxel (performed for the 5 subjects for whom we had the additional movie segments). As shown in Supplementary Figure 4*C*, this distribution is very close to the relevant Student's *t*-distribution. For example, for the threshold value $t_c = 3.7$, which corresponds to $P = 0.0104$ under Student's t_4-distribution, the empirical distribution yields $P = 0.098$. The differences are extremely small, although the Student's distribution provides conservative *P* values.

The statistical significance map of the group-level analysis was corrected for multiple comparisons through an adaptive, 2-stage FDR-controlling procedure at level $q = 0.15$ (Benjamini, Krieger, and Yekutieli 2005b). We indicate the level of $q = 0.05$ at the color bar of the group-level map in Figure 1*B*. Because the focus of this article is on

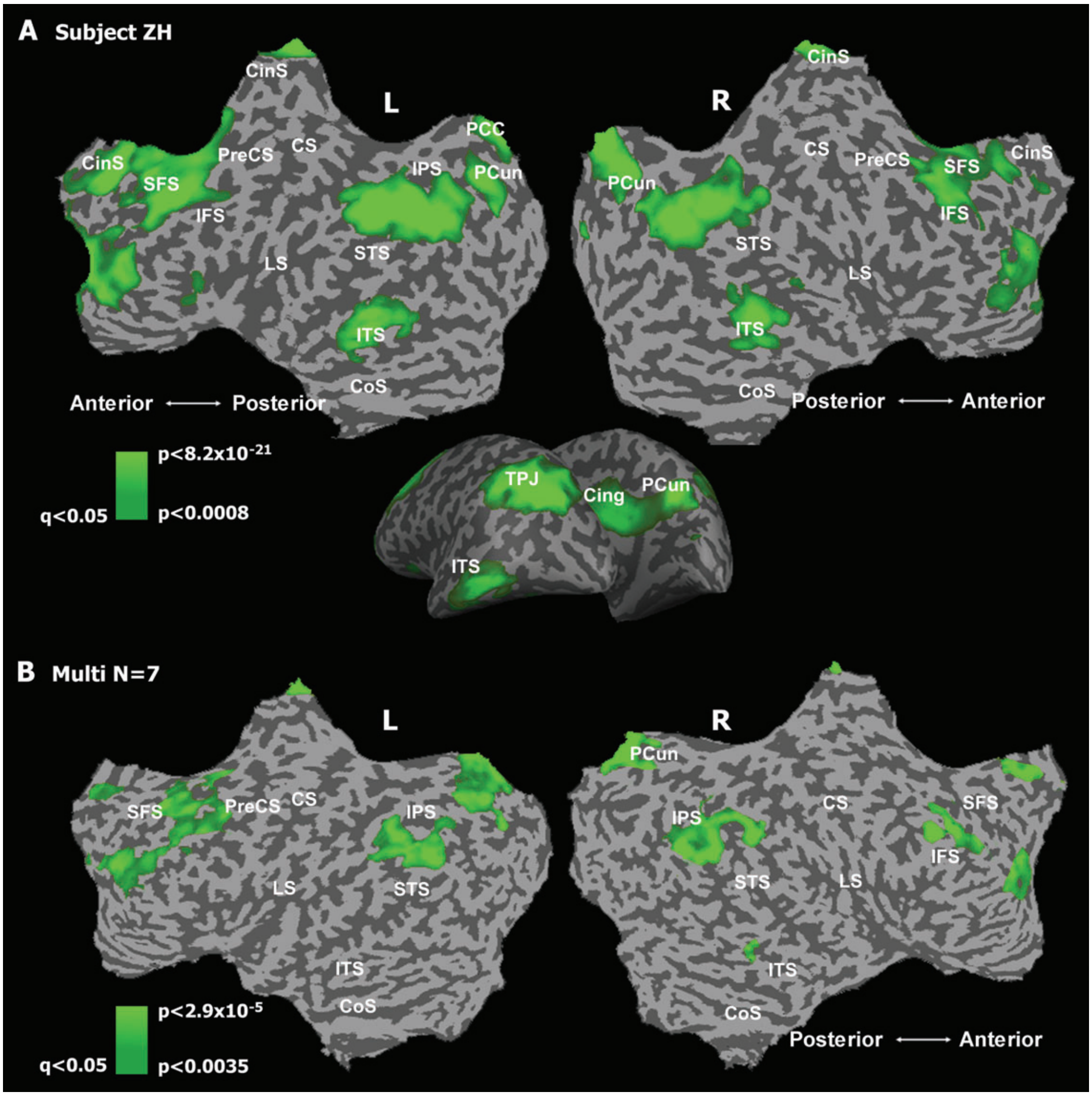

Figure 2. Neuroanatomical organization of functional connectivity analysis in the repeated movie paradigm. (*A*) Single-subject seed ROI analysis. Single-subject map showing correlation of every voxel in one of the hemispheres with the average seed time course from the opposite hemisphere. Seed ROIs consisted of ~10 contiguous voxels in the IPC that exhibited the minimal level of intrasubject correlation. The analysis was done for both hemispheres and averaged across 2 movie presentations per subject. The color scale indicates *t*-value significance level (left [L] hemisphere: $P < 0.0008$, q(FDR) < 0.05; right [R] hemisphere: $P < 0.0007$, q(FDR) < 0.05). (*B*) Group analysis. Neuroanatomical distribution of regions showing functional connectivity as revealed by multi-subject ($N = 7$), random-effect GLM analysis (L hemisphere: $P < 0.0035$, q(FDR) < 0.05; R hemisphere: $P < 0.0037$, q(FDR) < 0.05). Anatomical abbreviations are as in Figure 1.

the posterior cortex systems, this analysis was restricted to the caudal voxels, lying posterior to the central sulcus.

Functional Connectivity Analysis

Functional connectivity based on the "seed" time course was explored in the repeated movie, rest, and visual localizer experiments. Seed regions of interest (ROIs) in all these experiments were anatomically confined to the most consistent of the uncorrelated regions, the bilateral IPC, based on the results of the intrasubject correlation analysis, described in the previous section. The subject-specific seed ROIs were obtained by selecting in each hemisphere ~10 voxels with the lowest level of intrasubject correlation.

To perform the functional connectivity analysis, seed time series for each movie session were extracted for the subject-specific ROIs in the bilateral IPC by averaging the time series of all voxels in the ROI. To minimize hemisphere-specific effects, seed time series from one hemisphere was used as a predictor for the activity in the contralateral hemisphere (as can be seen in Fig. 3, the connectivity pattern was largely symmetrical in both hemispheres). The resulting time series were then used as a covariate of interest in linear regression analysis, after removal of the auto-regression factor (AR(1) model), performed on each movie session separately and later combined. Individual contrast images corresponding to this covariate were corrected for multiple comparisons by controlling the FDR at the 5% level, as described in the previous section. The mean significance cutoff *t*-value of this analysis was $t_c = 3.3$.

Individual contrast images were entered into a second-level random-effect analysis to determine the brain areas that showed significant functional connectivity across subjects (Figs 2*B* and 3*B*). The final map reflects regions whose activity is correlated to the activity in the seed ROI (here IPC) across subjects. FDR control of the random-effect group analysis was achieved by using the repeated experiment procedure of Benjamini and Yekutieli (2005a) (see also Reiner and others 2003), utilizing the 2 movies one at a time sequentially. That makes use of the fact that results for the 2 movies are independent of each other. Using the data for the first movie only, voxels significant at FDR level $q_1 = 2/3$ were kept for further analysis. This limited set of voxels was now tested using the second movie data, and the BH procedure was now used at

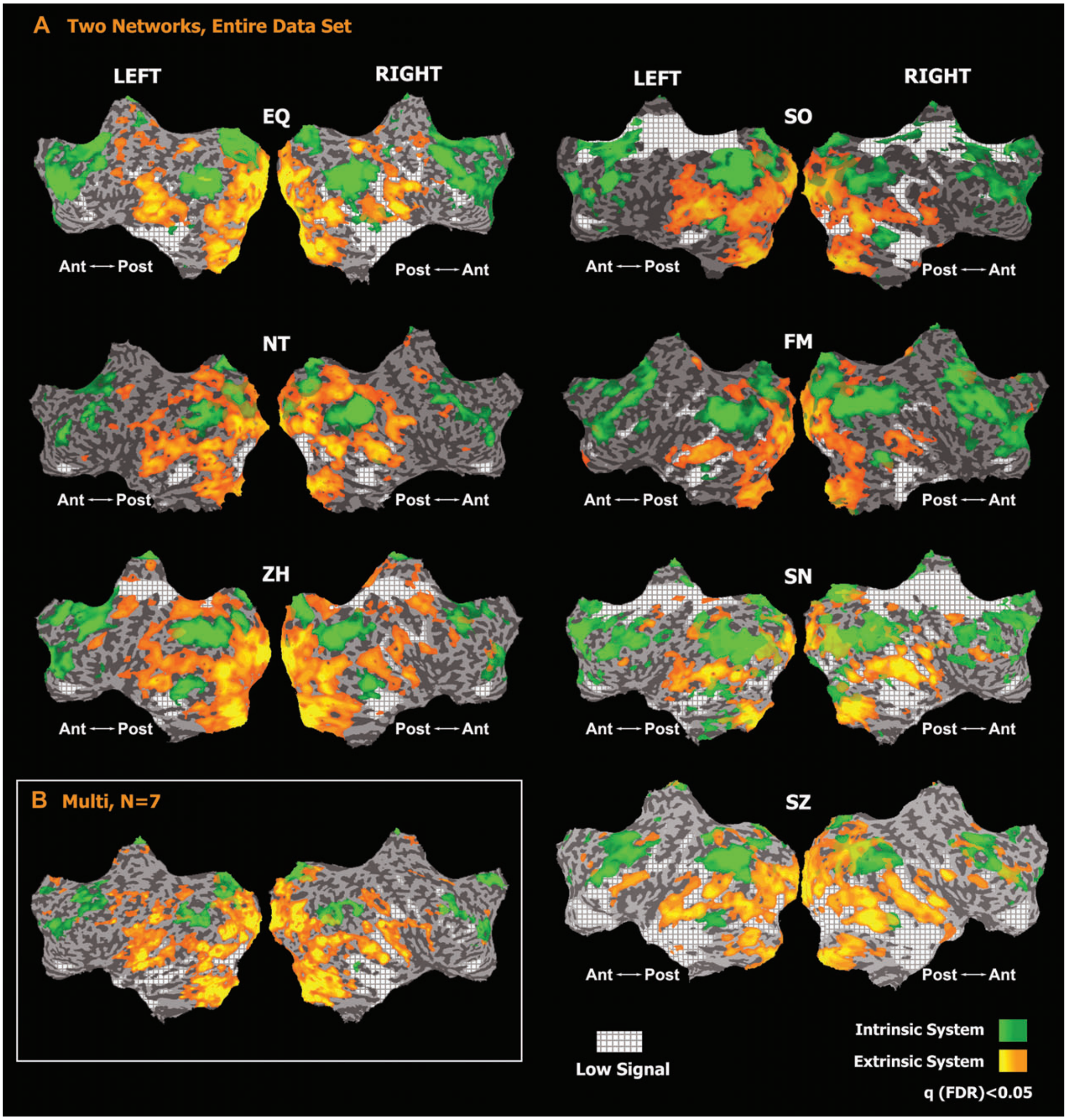

Figure 3. Neuroanatomical distribution of the extrinsic and intrinsic networks. The extrinsic network of areas (orange to yellow, see Fig. 1) exhibited correlated neuronal dynamics across repeated movie presentations. The activity of the intrinsic network (light-green to green, Fig. 2) was decoupled from external stimulation. In addition, regions in which the BOLD signal was low due to magnet limitations (gray plaid) were added to the map. Note that the 2 networks largely complement each other and together cover almost the entire extent of the posterior cortex. (*A*) Single subjects (q(FDR) < 0.05). (*B*) Multi-subject ($N = 7$) groupwise t-statistics image (extrinsic: q(FDR) < 0.15, intrinsic: q(FDR) < 0.05).

$q_2 = 0.075$. This resulted in an overall FDR for the final set of voxels of $q = 0.05 = q_1 \times q_2$ because of the independence of the test statistics based on the 2 movies (for proof and details, see Benjamini and Yekutieli 2005a).

Additionally, we performed the functional connectivity analysis in the repeated movie paradigm, without global signal removal. This was done in order to examine the potential impact of this preprocessing stage. As can be seen in Supplementary Figure 4, the global signal removal did not change the connectivity pattern.

In order to evaluate the amount of cortex covered by the 2 networks, we mapped the regions in which the BOLD signal was exceedingly low, due to anatomical characteristics of the human brain and scanning disturbances (Fig. 3). Voxels in which averaged signal amplitude across time was lower than 0.15 of the maximum mean signal amplitude across all voxels (per subject) are marked as "low signal" in Figure 3.

In the functional connectivity analyses of the rest and visual localizer experiments, FDR correction procedure did not reveal significant activation, possibly due to intersubject variability and limited number of subjects. Therefore, these maps (Fig. 5) are presented at the uncorrected $P < 0.005$. In addition, we supply FDR-corrected individual subjects' results in Supplementary Figure 5.

Definition of ROIs and Time Course Analysis

In order to estimate the degree of signal modulation in the extrinsic and intrinsic systems, 3 functional regions in the extrinsic system were defined. To this end, we applied general linear model (GLM) analysis to the visual localizer experiment. Two face-related and one building-related regions were localized by contrasting face and building coefficients, while disregarding the other conditions ($P < 0.05$, corrected). Two face-related regions were confined to the fusiform face area (FFA) (Kanwisher and others 1997; Malach and others 2002) and the face-selective region in the vicinity of lateral occipital sulcus (Malach and others 2002; Hasson and others 2003). The building-related ROI was similarly defined in the collateral sulcus (Levy and others 2001; Malach and others 2002).

In order to examine the correlation across the 2 movie presentations at the network level (Fig. 4*A*,*B*), we calculated average signal from the entire intrinsic and extrinsic systems. In the extrinsic system, the average signal was sampled from all the regions showing significant level of intrasubject correlation. In the intrinsic system, the average signal was sampled from all the regions showing significant level of functional connectivity (these intrinsic and extrinsic regions are presented in Fig. 3). The time series of each anatomical region were averaged across hemispheres, *z* normalized, and then averaged across regions, therefore providing one time series per run, per network. The network-level correlation across movie presentations (Fig. 4*B*) was calculated on these time series.

Additionally, we calculated the average correlation within and across networks. Due to computational limitations, the volumetric cortical space of each network was reduced by averaging every 20 adjacent voxels. The average correlation of all pairwise combinations of these average voxels within and across networks was calculated. Coefficients were then averaged into 3 groups (Fig. 4*C*): extrinsic denotes correlations between the extrinsic regions. Intrinsic denotes correlations between the intrinsic regions. Finally, extrinsic/intrinsic represents an average of all the across-networks correlations.

Activation/Deactivation Profiles in the Visual Localizer

In order to assess the selective activations and deactivations elicited by the experimental conditions of the visual localizer experiment, we applied GLM approach (Friston 1995). The hemodynamic delay of 3 or 6 s was chosen individually for a best fit to the task waveform. A boxcar predictor was constructed for each experimental condition, and the model was independently fitted to the time course of each voxel. A coefficient was calculated for each predictor using a least-squares algorithm. After computing the coefficients for all regressors, we performed a 2-tailed *t*-test of all visual conditions versus fixation using a random-effect model (Fig. 6, $P < 0.001$, uncorrected).

Results

Mapping Subject-Specific Movie-Related Activity

In order to identify all the regions engaged by movie-related processing, including subject-specific processing, we used the natural viewing paradigm as in Hasson and others (2004) and extended it to apply a within-subject analysis. In the repeated movie experiment, we presented the same movie segment twice to the same subject and calculated the correlation coefficient of time course of activity of each cortical voxel across the 2 presentations of the same movie (supplementary Fig. 1). We assumed that the correlation coefficient of each voxel could be used to quantify the degree of its engagement in the consistent processing of the sensory input. Hence, mapping the correlation coefficients over the subject's cortex, we could delineate the extent of the movie-driven activity in the cortical space. We will refer to the correlation across movie sessions as the "intrasubject" correlation. It should be emphasized that this mapping does not depend on preexistent knowledge of the exact source of the activity (i.e., what specific aspects of the movie elicited the activation). Furthermore, because the correlation map was obtained separately within each individual subject, neither the functionality of the identified areas nor their neuroanatomical distribution was affected by the intersubject variability.

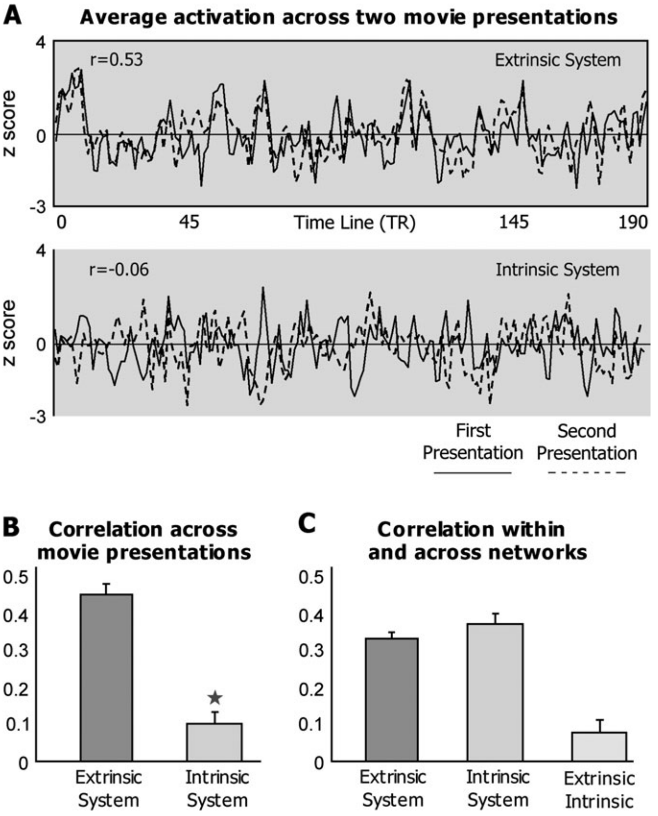

Figure 4. Activity profiles in the extrinsic and intrinsic networks. (*A*) Average activity in the extrinsic and intrinsic systems during 2 movie presentations. Note that the average activity in the extrinsic system was much more time locked to the movie ($r = 0.53$) compared with the average activity in the intrinsic system ($r = -0.06$). (*B*) Average intrasubject correlation. When averaged across subjects, the correlation across 2 movie presentations was significantly higher in the extrinsic network ($r = 0.44 \pm 0.03$) than in the intrinsic network ($r = 0.1 \pm 0.03$, $P < 0.0005$ paired *t*-test). Shown are the mean correlation coefficients of the average activity in the 2 systems. (*C*) Correlations within and across networks. Extrinsic and intrinsic denote mean correlation of activity within the extrinsic and the intrinsic systems, respectively. Extrinsic/intrinsic denotes mean correlation of activity across these 2 networks. As can be seen, there was no correlation across the time course of activity in these 2 systems ($r = 0.09 \pm 0.04$, $P < 0.067$), whereas the correlation among different voxel's signals within these systems was similar ($P < 0.1$).

The results of this analysis are depicted in Figure 1. We applied a nonparametric method for assessing the statistical significance of the correlations on the map and to create the statistical significance maps for single subjects. The map of the average correlation coefficient across subjects for each voxel and its statistical significance using *t*-tests (see Materials and Methods) are presented in Figure 1*B*. As expected from earlier studies (Hasson and others 2004), most regions in the posterior cortex showed a high level of correlation across movie sessions indicating that the movie produced consistent, time-locked modulation of activity in these areas. The cortical areas that showed significant levels of intrasubject correlation are listed in Table 1.

Within the large expanse of correlated activity, there were regions that consistently showed low levels of intrasubject correlation. The anatomical location of these regions was largely consistent across individual subjects. In the posterior cortex, these regions were confined to 3 main areas in the proximity of posterior cingulate cortex (PCC)/precuneus(PCun), inferior parietal cortex (IPC), and an isolated region in the inferior

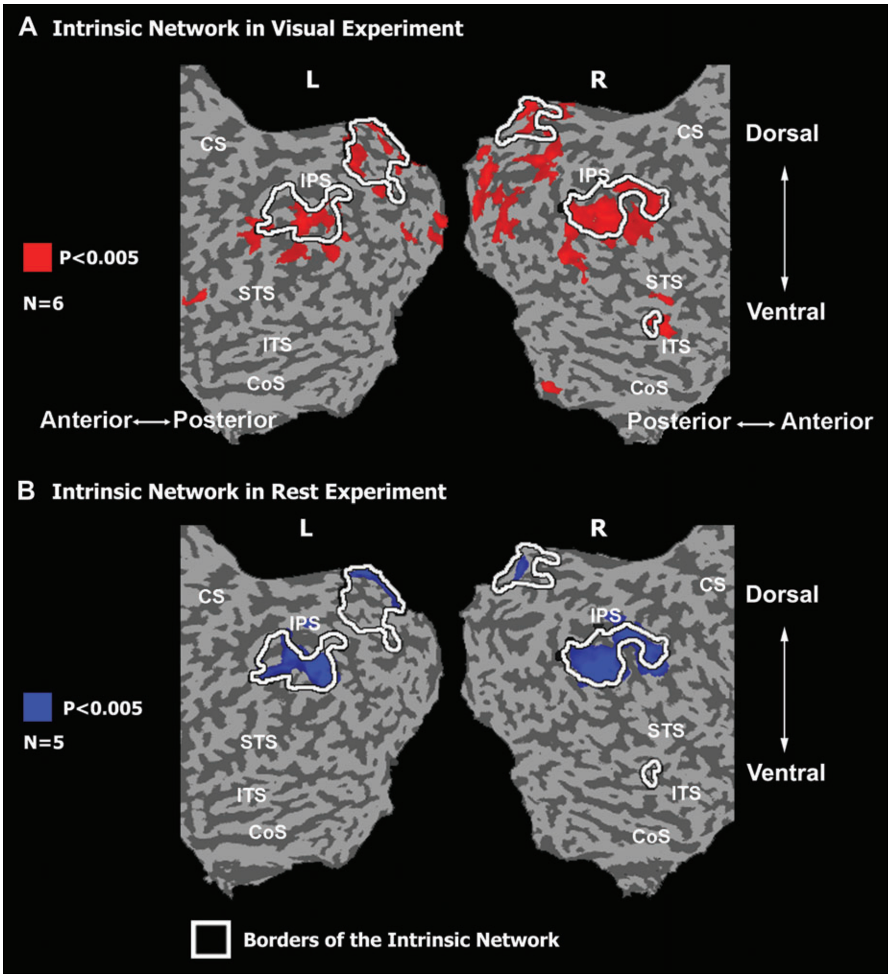

Figure 5. (*A*) Intrinsic network in standard visual experiment. (*B*) Intrinsic network during rest experiment. Functional connectivity patterns are presented on the posterior part of an unfolded cortex. Functional connectivity maps were calculated as in Figure 2, using the same seed ROIs in the IPC (random effect, $P < 0.005$, uncorrected). White lines mark the boundaries of the intrinsic network as defined in the repeated movie paradigm. Notice that the neuroanatomy of the intrinsic network appears to be roughly consistent across different experimental conditions. No consistent negatively correlated areas were detected in these analyses. Anatomical abbreviations are as in Figure 1.

lateral temporal cortex (ITC), bounded by the upper bank of the inferior temporal sulcus and the occipitotemporal sulcus, bilaterally (Fig. 1, depicted by arrows). Critically, these regions were consistently localized across individual subjects and were highly compatible with the regions that did not exhibit intersubject correlations (Hasson and others 2004).

In order to further validate the capability of the correlation mapping to distinguish between functionally distinct regions, we calculated intrasubject correlation between activity elicited by a movie segment described above and activity elicited by an identical movie segment but with no audio input (this analysis was done for 2 subjects). As expected, the resulting intrasubject correlation maps were highly similar to the ones produced by the audiovisual movie in the visual and parietal regions, but no correlation was evident in the auditory cortex, in the proximity of lateral sulcus and superior temporal gyrus (Supplementary Fig. 2).

Mapping Movie-Unrelated Activity

The analysis described above showed that there were anatomically well-defined regions in the posterior cortex, which did not show a consistent modulation by external audiovisual stimuli. However, the absence of intrasubject correlations does not imply that there was no spontaneous (uncorrelated) signal modulation in these regions during stimulation. In order to examine whether the regions that were not consistently modulated across movie sessions form, indeed, a functionally connected network, we examined to what extent the activity in these regions was similarly modulated within a single session. This was done using functional connectivity analysis based on a seed time course (Friston and others 1993; Biswal and others 1995; Lowe and others 1998; Greicius and others 2003).

Seed ROIs were defined for each subject, in each cerebral hemisphere, as clusters of ~10 contiguous voxels showing the least intrasubject correlation across the 2 movie presentations. They were anatomically confined to the most consistent of the uncorrelated regions, the IPC. Regions showing high temporal coherence were assumed to form a functionally connected network (Lowe and others 1998). The results of this analysis superimposed on the 2 unfolded cortical hemispheres are shown in Figure 2 for a single subject (*A*) and for the group average (*B*). In the prefrontal cortex, the temporal coherence with the IPC was found in ventral medial areas (Brodmann area BA 10) and dorsal areas located in the proximity of middle frontal gyrus (BA 8). In the posterior parts of each hemisphere, 3 main regions exhibited high functional connectivity.

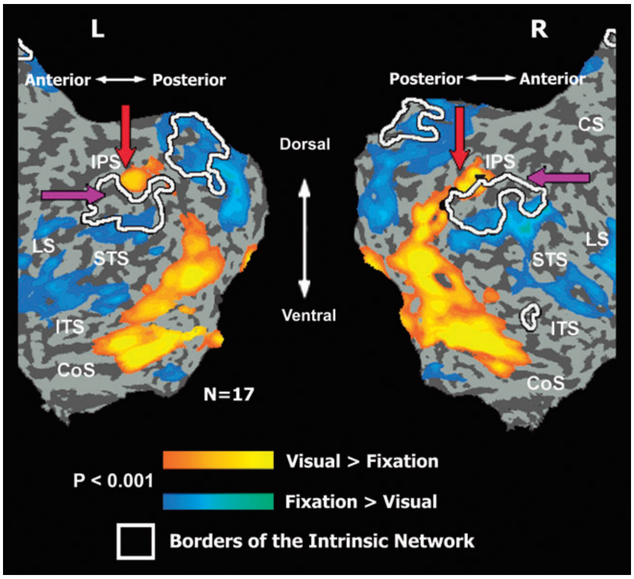

Figure 6. Deactivations in the posterior cortex during visual stimulation. Average activation (orange-yellow) and deactivation (blue-green) maps in visual, block-designed experiment (random-effect GLM, 17 subjects, $P < 0.001$, uncorrected) presented on the posterior part of an unfolded cortex. White lines mark the boundaries of the intrinsic network as defined in the repeated movie paradigm. Many deactivation patches could be found within the boundaries of the intrinsic network. Purple arrows mark the anterior region of the intrinsic region in IPC, which was not significantly deactivated by visual input. Notice the remarkable interdigitation in the parietal cortex (marked by red arrows), between the intrinsic patches and the visually driven areas. Anatomical abbreviations are as in Figure 1.

Table 1
Cortical areas of high intrasubject correlation

	Approximate BAs	Number of hem (L/R), $N_{\max} = 7$
Visual cortex		
Early visual areas	17, 18	7/7
Visual association cortex	19, 37	7/7
Parietal cortex		
Superior parietal	7	4/4
Postcentral	1, 2, 3	5/3
Auditory/language cortex		
Superior temporal cortex	41, 42, 22, 21	7/7
Prefrontal cortex		
Superior precentral sulcus	6	5/5
Inferior frontal gyrus	44	5/3

Table 2
Talairach coordinates of intrinsic regions in the posterior cortex

	Left hemisphere				Right hemisphere			
	Number	x	y	z	Number	x	y	z
IPC	7	−38 ± 3	−60 ± 6	36 ± 4	7	39 ± 5	−54 ± 4	39 ± 4
PCC/PCun	7	−8 ± 4	−55 ± 5	32 ± 4	7	4 ± 2	−52 ± 4	30 ± 3
ITC	4	−55 ± 3	−45 ± 6	−9 ± 5	5	50 ± 9	−37 ± 6	−6 ± 6

Note: Average Talairach coordinates of brain regions that showed significant connectivity to the contralateral seed in IPC. Numbers are in mm ± SD.

Interestingly, these regions were located in the proximity of PCC/PCun, IPC, and ITC and showed complete overlap with the regions whose activity was not correlated across sessions. In other words, regions showing low levels of intrasubject correlation (therefore, regions which were probably not associated with the processing of the movie) were found to be functionally interconnected. (See Table 2 for Talairach coordinates of regions in the posterior cortex which showed temporal coherence to IPC.) No regions showing significant negative correlation to the IPC seed were detected in the group analysis.

In order to examine the neuroanatomical relationships between the externally (movie) driven system of sensory areas (heretofore extrinsic) and the areas that showed movie-independent activity (heretofore intrinsic), we superimposed these 2 networks on the cortical surface. As can be seen in Figure 3, these 2 networks revealed a striking neuroanatomical complementarity and together provided almost a complete coverage of the posterior cortex (Fig. 3).

Interestingly, in the prefrontal cortex, in contrast to the caudal parts of the brain, the intrinsic system seemed to be more extended than the extrinsic system. To evaluate the reliability of this observation, we calculated the number of voxels associated with both of these networks in the frontal parts of the cortex (anterior to the central sulcus). Indeed, the number of the intrinsic voxels was significantly higher than the number of the extrinsic voxels (mean ratio intrinsic/extrinsic is 13.7 ± 1, $P = 0.0001$ using 2-tailed *t*-test on log ratios).

Comparing Activity in the Intrinsic and Extrinsic Systems

To further understand the function of the areas associated with the intrinsic network, we examined to what extent these areas were modulated during the presentation of the movie. For that purpose, we compared the degree of signal fluctuations in the intrinsic and extrinsic systems. Signal fluctuation was estimated by measuring the variance of the time courses sampled from distinct regions comprised by the 2 systems. Variance per subject per network was calculated by averaging the variance from 3 extrinsic regions in the ventral pathway and 3 posterior intrinsic regions separately (see Materials and Methods). This analysis revealed that the depth of modulations in these 2 systems was not significantly different (SD = 8.2 ± 0.43 and SD = 8.9 ± 0.46 for the intrinsic and extrinsic systems, respectively; $P = 0.23$ using 2-tailed paired *t*-test for SD difference on logarithmic scale). This result suggests that during movie presentation, the signal in the intrinsic system was not flat but rather showed spontaneous modulations that were similar in magnitude to the sensory-driven modulations found in the extrinsic system.

We further examined the time courses of voxels in the extrinsic and intrinsic systems sampled from all the areas comprised by each network (Fig. 4*A*,*B*). Close inspection of the time courses revealed that the average signal in the extrinsic system indeed showed a significantly higher correlation across sessions (i.e., more synchronized with the movie and therefore across sessions) than the average signal in the intrinsic system (Fig. 4*B*; mean correlations of 0.44 ± 0.02 and 0.1 ± 0.03 for the extrinsic and intrinsic systems, respectively; $P < 0.0005$ using paired *t*-test; see Fig. 4*A* for single-subject time courses).

In addition, we calculated the average correlation of time course of activity across and within the 2 systems (see Materials and Methods). As evident in Figure 4*C*, the 2 networks exhibited spatial decoherence, that is, there was no correlation across the time course of activity in these 2 systems ($r = 0.09 \pm 0.04$, $P < 0.067$). In contrast, the average correlation of activity within the same system was similar in the extrinsic and intrinsic systems ($r = 0.34 \pm 0.02$ and $r = 0.37 \pm 0.03$, respectively).

To conclude, the time course analyses within and across subjects indicate that the intrinsic system was indeed active during movie presentation, but this activity was not locked to the external stimulation.

The Intrinsic System Is Not a Peculiarity of the Movie Presentation Paradigm

The previous analyses showed that the neuroanatomy of the intrinsic system is consistent across subjects (see Figs 2 and 3). Although these findings strongly suggest the existence of a functionally distinct neural network, it could be the case that this network is specific to our experimental paradigm. In order to explore this possibility, we applied functional connectivity analysis in 2 additional experimental paradigms in the same subjects. Functional connectivity was assessed in a standard, block-designed visual localizer experiment, using object images of various categories and in a passive rest experiment. In the rest experiment, the subjects simply laid in the darkness with their eyes closed. The seed ROI for these analyses was the same as that used in the repeated movie presentation experiment. The full, single-subject data set for these 2 experiments is presented in Supplementary Figure 5. As can be seen in the group analysis, presented in Figure 5, the spatial distributions of functional connectivity maps in the visual experiment and in the rest experiment were similar to the intrinsic network revealed in the repeated movie paradigm.

This pattern suggests that the functional connectivity of regions composing the intrinsic network is not specific to a particular experimental paradigm.

Comparison of the Intrinsic System to the Default-Mode System

Previous studies described a default-mode brain system (Gusnard and Raichle 2001; Raichle and others 2001) as a set of regions that show consistently higher activation in the absence of stimulation compared with when the subject is involved in a variety of perceptual and cognitive tasks (Shulman and others 1997; Mazoyer and others 2001). The neuroanatomical mapping of the default-mode system (Gusnard and Raichle 2001; Greicius and others 2003, 2004) appears to be similar to the intrinsic system identified in our experiment, comprising medial and lateral parietal areas, ITC, and medial prefrontal cortex.

To examine the relationship between the currently described intrinsic system and the previously described default-mode system, we overlapped the boundaries of the intrinsic system with the regions showing stronger activation during fixation than during visual stimulation. The latter regions were found in a previous block-designed visual localizer experiment (Hasson and others 2003) that included a large group of subjects ($N = 17$, 6 of these subjects participated in the repeated movie experiment). As evident in Figure 6, there was a substantial overlap between the intrinsic system (white boundary lines) and the regions inhibited by visual stimulation (green-blue). Note also the remarkable interdigitation in the parietal cortex between the borders of the intrinsic system (white boundary lines) and the sensory areas in the visual experiment (red arrows in Fig. 6). Some deactivations lying outside the borders of the intrinsic system were detected, especially in the auditory cortex and language-related regions in the anterior and posterior superior temporal sulcus. However, the deactivations in these regions were shown to be task specific (Shulman and others 1997; Amedi and others 2005) and therefore are not part of the default-mode regions.

It should be noted that an overlap in the intrinsic region in the IPC was evident in its posterior parts only, whereas more anterior areas, protruding into the lateral aspects of the intraparietal sulcus (BA 40), were not consistently deactivated by visual stimulation (see purple arrows in Fig. 6).

To further examine the similarity of these 2 systems, we compared the functional connectivity map of the intrinsic system as defined from the uncorrelated voxels in the repeated movie paradigm (Fig. 2) with functional connectivity map using the deactivation patches in IPC (Fig. 6) as a seed ROI. The seed ROIs were sampled from the right hemisphere because the deactivation regions were more consistent in the right hemisphere. Therefore, the results of this analysis are shown for left hemisphere only in Supplementary Figure 6. This allowed us to compare the definition of the intrinsic and the default-mode systems within the framework of identical analysis. The results of this analysis revealed largely similar connectivity maps.

Overall, there seemed to be substantial overlap between the intrinsic system, revealed by its dissociation from external stimulation, and the task-negative default-mode brain regions.

Discussion

Two Functional Networks in the Posterior Cortex

The most important outcome of this study was the identification of 2 intertwined global functional systems in the posterior cortex under natural sensory stimulation. During continuous audiovisual stimulation, the overall activity across these 2 systems was decoupled, whereas the activity within each of these 2 systems was correlated. The first system manifested high levels of correlation across repeated sensory inputs (within-subject correlation). We assume that this system is consistently modulated by external sensory stimulation, and we coined it extrinsic. In contrast, the second system, which we termed the intrinsic system, was characterized by low levels of within-subject correlation across the 2 presentation of the same movie segment, and therefore, we assume that it is relatively decoupled from the external stimulation. However, it should be emphasized that the intrinsic system was active during audiovisual stimulation, as reflected by similar levels of signal fluctuations in these 2 systems.

The functional neuroanatomy of the extrinsic system was extensively investigated and amply documented (Ungerleider and Mishkin 1982; DeYoe and others 1994; Grill-Spector and Malach 2004). Despite the global temporal coherence in its activity, the extrinsic system could be subdivided into different functional components, such as visual, auditory, and somatosensory (Hasson and others 2004; Fig. 1). In contrast, the various subdivisions of the intrinsic system have not been fully delineated yet. The present results show that this system includes several consistent regions in the prefrontal and posterior cortex. In the prefrontal cortex, which is presumably associated with high-order, self-related functions, the proportion of voxels associated with the intrinsic system was higher than the proportion of voxels associated with the extrinsic system. In the present study, we focused, however, on the posterior cortical regions. Here the intrinsic system was constrained to 3 isolated islands in each hemisphere: the PCC/PCun, the IPC, and an isolated region in the ITC (Fig. 2). Although the activity in these regions was not correlated across the 2 movie presentations either across or within participants, they were highly correlated among themselves.

A further, anterior–posterior functional subdivision of the inferior parietal region was evident in the visual localizer experiment. The posterior part of IPC (angular gyrus, BA 39) was deactivated by visual input in a standard visual experiment. In contrast, the more anterior part of IPC, protruding into the lateral bank of the intraparietal sulcus (BA 40) did not seem to be consistently deactivated by sensory input (Fig. 6).

From a global neuroanatomical point of view, two additional points should be emphasized. First, the territories of the 2 systems were largely interdigitated, that is, most of the regions belonging to the extrinsic and intrinsic systems did not overlap. Second, together these 2 networks appeared to account for essentially the entire extant of the posterior cortex (Fig. 3). There were, however, some exceptions to this rule. For example, the entorhinal cortex and anterior parahippocampal gyrus did not manifest clear association with either system. These cortical regions are part of the medial temporal lobe memory system (Mishkin and others 1997). Therefore, it is not clear to what extent these regions should be consistently activated during sensory stimulation tasks. Previous studies suggest that these areas maybe, at least partially, associated with task-negative behaviors (Stark and Squire 2001; Greicius and others 2004).

The importance of finding global cortical subdivisions goes beyond the mere neuroanatomical delineation because such partitions might manifest essential principles of functional organization. From this perspective, the intrinsic system is likely to have a fundamental function, as important as that of the extrinsic system, which is involved in processing sensory inputs.

Comparison with ''Default-Mode'' Studies

Apart from being attentive to the outside world, the human mind is engaged by internally initiated mental processes. An important example of such intrinsic functionality is task-unrelated thoughts (TUTs), which have been termed the default mode of operation of the self-aware mind (Singer 1978; Giambra 1995). Several studies have shown that when externally implied demand for processing capacity is diminished, the intensity of TUTs increases (Antrobus and others 1966; Antrobus 1968; Teasdale and others 1995; McKiernan and others 2006). From that perspective, a reasonable situation for exploration of the internal stream of consciousness is the passive rest state, in which no external task or information is present.

Recent studies indeed revealed a network of regions, which appears to be associated with activity during a resting state (Gusnard and Raichle 2001; Raichle and others 2001; Greicius and others 2003, 2004; Burton and others 2004). These regions were shown to be more active during rest or passive tasks than during a large array of goal-directed tasks (Shulman and others 1997; Mazoyer and others 2001; McKiernan and others 2003). Additionally, functional connectivity studies during rest have shown that these regions provide an interconnected network of regions, comprising medial and lateral parietal areas, ITC, and medial prefrontal cortex (e.g., Greicius and others 2003). According to this activation profile, this network was hypothesized to bear a default-mode function, that is, an organized cognitive activity involving a variety of self-initiated internal processes and that this activity is interrupted by externally induced demands.

The neuroanatomical distribution of the intrinsic system, as found in the present study, largely overlaps with the default-mode network of regions as reported in the literature. Similarly, we showed that major parts of the intrinsic system also tend to exhibit deactivations during visual stimulation in a standard, block-designed visual experiment (Fig. 6). Therefore, this study demonstrates a convergence of 2 different paradigms in the definition of neural network that seems to support internally oriented processing.

It should be noted that the default-mode or "task-negative" system was recently reported to be inversely related to the global network of regions in the parietal and frontal cortices during passive rest state condition (Fox and others 2005; Fransson 2005). In the present study, we have failed to observe such negative correlation between the extrinsic and the intrinsic systems (for similar results, see also Nir and others 2006). Also, in the study of Fox and others (2005), early sensory areas were not found to be functionally connected to the "task-positive" system—which overlaps parts of the extrinsic system reported here. These interesting differences are likely due to task differences, that is, rich sensory stimulation versus rest, but other factors such as differences in signal processing, for example, in the estimation of the global brain signal or in the temporal filtering during preprocessing stages, may have contributed to these differences as well.

Intrinsically Oriented Processing

As suggested above, the intrinsic system appears to manifest internally oriented mental processes. What could these processes be? Some previous suggestions included the following: a continuous perspective of the organism onto its environment (Gusnard and Raichle 2001; Raichle and others 2001), self-referential processing (Northoff and Bermpohl 2004; Gusnard 2005), problem solving and task-independent thoughts (Binder and others 1999; McKiernan and others 2006), episodic memory (Greicius and others 2003, 2004; Greicius and Menon 2004), first-person perspective (Vogeley and Fink 2003), social cognition, and a sense of agency (Decety and Sommerville 2003; Gallagher and Frith 2003). Thus, an impressive number of studies showed the involvement of areas overlapping the intrinsic system—in functions which appear to be associated, at least partially, with some aspects of intrinsically oriented functions (Burgess and others 2001; Ruby and Decety 2001; Vogeley and others 2001; Chaminade and Decety 2002; Kjaer and others 2002; Lou and others 2004). However, it should be noted that many of these studies were based on comparison between task-positive conditions, rather than direct comparison with the baseline, task-negative condition. In fact, when tested, these studies often revealed differential deactivations rather than positive (above rest) activations in the default-mode structures (Northoff and Bermpohl 2004).

In conclusion, it seems that regions comprised by the intrinsic system are associated with a multitude of complex internal processes. Additional work, however, is required to discover the precise nature of these processes.

A Hierarchy of Cortical Subdivisions

To summarize, we provide further support for the notion that a major, large-scale subdivision should be incorporated into descriptions of the functional organization of the human cortex. Considering the global organization of the cortex, a hierarchical sequence of subdivisions can be discerned (Fig. 7). At the top, a natural split has been traditionally assigned to the division between the posterior cortex engaged mainly by input, that is,

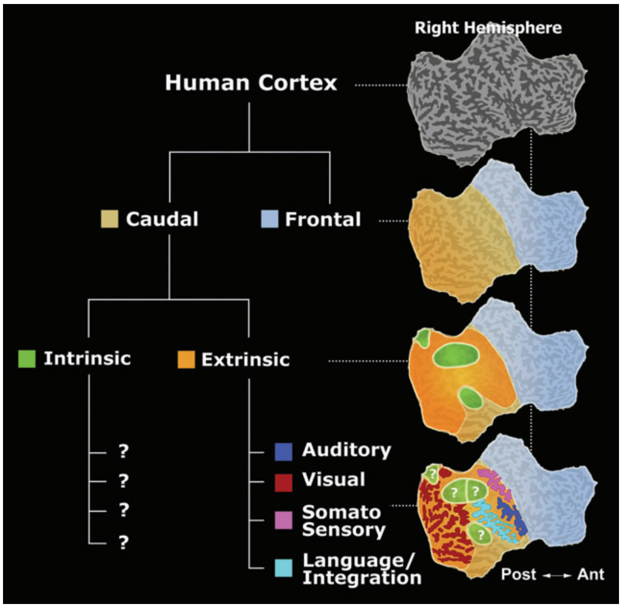

Figure 7. Neuroanatomical partition of the posterior cortex into extrinsic and intrinsic systems. A global schematic framework of subdivisions is proposed. The suggested large-scale dividing line defines a bipartite organization of the posterior cortex into a system of regions related to sensory processing—the extrinsic network and the intrinsic network of regions that likely relate to internal processing but whose exact functional nature is still enigmatic.

sensory processing, and the frontal cortex devoted largely to output, that is, executive functions (Stuss and Benson 1986; Stuss and Knight 2002; Wood and Grafman 2003). Below this global subdivision, the present study supports a further subdivision of the cortex (for supportive results, see Fox and others 2005) into a bipartite organization, consisting of 2 complementary systems. First, the extrinsic system is dedicated to processing of external stimuli. This system is well studied and can be further subdivided functionally into auditory (Formisano and others 2003), visual (Van Essen and others 2001; Malach and others 2002), somatosensory (Roland and others 1998; Polonara and others 1999), and language/integration areas (Wise and others 2001; Beauchamp and others 2004). Its complementary system, the intrinsic system, likely deals with complex internal mental processing. This system largely overlaps the default-mode network (Gusnard and Raichle 2001; Raichle and others 2001) and still remains to be fully elucidated. Together the 2 systems comprise essentially the entire territory of the posterior cortex. Thus, the model that incorporates the extrinsic–intrinsic dimension, as proposed in the current study, summarizes many local findings into a hierarchy of functional areas that together comprise essentially the entire territory of the posterior cortex.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Notes

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