Brain dynamics during natural viewing conditions—A new guide for mapping connectivity in vivo

Andreas Bartels* and Semir Zeki

Wellcome Department of Imaging Neuroscience, University College London, London, UK

We describe here a new way of obtaining maps of connectivity in the human brain based on interregional correlations of blood oxygen level-dependent (BOLD) signal during natural viewing conditions. We propose that anatomical connections are reflected in BOLD signal correlations during natural brain dynamics. This may provide a powerful approach to chart connectivity, more so than that based on the 'resting state' of the human brain, and it may complement diffusion tensor imaging. Our approach relies on natural brain dynamics and is therefore experimentally unbiased and independent of hypothesis-driven, specialized stimuli. It has the advantage that natural viewing leads to considerably stronger cortical activity than rest, thus facilitating detection of weaker connections. To validate our technique, we used functional magnetic resonance imaging (fMRI) to record BOLD signal while volunteers freely viewed a movie that was interrupted by resting periods. We used independent component analysis (ICA) to segregate cortical areas before characterizing the dynamics of their BOLD signal during free viewing and rest. Natural viewing and rest each revealed highly specific correlation maps, which reflected known anatomical connections. Examples are homologous regions in visual and auditory cortices in the two hemispheres and the language network consisting of Wernicke's area, Broca's area, and a premotor region. Correlations between regions known to be directly connected were always substantially higher than between nonconnected regions. Furthermore, compared to rest, natural viewing specifically increased correlations between anatomically connected regions while it decreased correlations between nonconnected regions. Our findings therefore demonstrate that natural viewing conditions lead to particularly specific interregional correlations and thus provide a powerful environment to reveal anatomical connectivity in vivo.
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* Corresponding author. Present address: Max Planck Institute for Biological Cybernetics, Spemannstr. 38, 72076 Tübingen, Germany. Fax: +49 7071 601 652.

E-mail address: andreas.bartels@tuebingen.mpg.de (A. Bartels).

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Introduction

Much of the brains structure and connectivity have evolved to deal with the dynamic complexity of natural conditions, which govern brain states of considerable parts of our waking time and also influence the brain during development. It thus seems likely that the study of functional activations and interregional interactions in these conditions may reveal basic principles of functional and structural brain organization. Our previous studies support this view. They revealed that distinct brain regions maintain or potentially even enhance their functional specificity during natural viewing conditions (Bartels and Zeki, 2003, 2004a). Our findings were confirmed by those of Hasson et al. (2004) and go beyond in emphasizing a surprisingly high degree of area-specific activity. Its extent is such that data-driven methods such as independent component analysis (ICA) can identify and segregate a multitude of distinct regions across the whole brain, even within the visual cortex, based solely on their characteristic activity time courses (ATCs) during natural vision (Bartels and Zeki, 2004a). This reveals a highly modular organization of brain function. Here we test our supposition that areas that have highly correlated ATCs are directly connected anatomically. This suggestion arose from our observation that despite the high degree of area-specific activity during natural conditions, some regions maintained spatially specific correlations with others and that this occurred consistently between regions that are known to be anatomically connected (see Results and discussion section, as well as Bartels and Zeki (2004a,b)). In the present study, we therefore wanted to examine our empirically inspired hypothesis that temporal correlations between distinct brain regions (i.e., functional connectivity (Friston et al., 1993)) during natural viewing conditions may be indicative of anatomical connectivity.

Conceptually, we hypothesize that communication between regions is likely to be 'visible' in the form of BOLD signal correlations especially during exposure to dynamic natural conditions. Synaptic input as well as spiking output (both conveyed by anatomical connections) are most correlated with synaptic activity, which is the best neurophysiological predictor of BOLD signal, during transients of stimuli (see e.g., Logothetis et al., 2001), such as occur during dynamic natural conditions. Traditional epoch- or event-related studies, in contrast, are usually

designed to engage only a subset of specialized regions in processing. They are thus ideally suited to reveal the modulation of connectivity strengths induced by particular tasks and stimuli of interest (Buchel and Friston, 1997; Friston and Buchel, 2000; Friston et al., 2003). This stands in contrast to the rich complexity of dynamic, natural stimuli that are likely to engage a much broader set of connections. The same caveats apply to both approaches, no matter whether controlled or natural stimuli are used, or whether the aim is to infer effective or anatomical connectivity. On the one hand, there may be spurious correlations, for example, induced in anatomically nonconnected regions by common vascularization from a third region or by coincidence. On the other hand, there may be a lack of correlation in BOLD signal between regions that do communicate because their BOLD signal does not reflect their neuronal input or output well. This highlights the obvious caution that even if functional connectivity during natural conditions should empirically prove to be indicative of anatomical connectivity, it can never replace anatomical tools, even though it may guide them. Whether the average correlations between brain regions during natural conditions may be indicative of anatomical connectivity remains thus to be tested empirically. But in a system such as the human cerebral cortex whose connectivity remains largely unknown and much of it remains inferential, an additional guide may be of complementary value.

There is a growing body of literature describing temporal correlations between distinct regions during the 'resting state' of the brain (Arfanakis et al., 2000; Biswal et al., 1995; Cordes et al., 2000, 2001; Hampson et al., 2002; Lowe et al., 1998; Van De Ven et al., 2004; Xiong et al., 1999). A usually implicit but sometimes explicitly stated idea is that resting state functional connectivity may be indicative of anatomical connections between functionally related regions, which is supported by the results obtained (see, e.g., Cordes et al., 2000; Hampson et al., 2002; Koch et al., 2002; Lowe et al., 1998; Quigley et al., 2003; Young et al., 2003). The 'resting state' is thought to reveal correlations that are not biased by specialized stimuli. Unfortunately, 'resting' or 'steady state' basically stands for 'unknown state.' Apart from emerging evidence for particular networks of regions whose activity may be specific to rest conditions (Raichle et al., 2001), the observed signal is likely to originate from mental imagery of undisclosed nature, unknown thought process, or preoccupations combined in an unknown way with spontaneous cerebral activity (Leopold et al., 2003). The interpretation of 'resting state' results, especially with regard to potential physiological explanations such as low-frequency oscillations observed in local field potentials (Leopold et al., 2003), is therefore problematic. Our hypothesis in this study is that exposing the brain to natural conditions will elicit equally unbiased and 'natural' brain dynamics as 'rest,' but with a more explicit understanding of the source of the signal and an improved signal-to-noise ratio and thus better chances of revealing neuronally specific interactions. Natural conditions will elicit higher neuronal activity variation than rest, thus increasing the functionally specific neuronal contribution to the total signal variation in relation to that of unspecific and nonneuronal sources. This should improve the sensitivity of the method in detecting functionally and anatomically connected regions. We therefore hypothesize that natural conditions should be superior to rest for the mapping of functional and anatomical connectivity.

A crucial question in this context is the degree of functional specialization of distinct regions or pathways. If perceptual analysis "...is performed interactively by areas and neurons with multi-purpose properties" (Schiller, 1997) one would expect an increase of correlations between visual areas during natural viewing, since then their 'multipurpose' characteristics would be interactively engaged. Our evidence points in the opposite direction, leading us to believe in a high degree of functional specialization (Bartels and Zeki, 1998; Zeki, 1978). Functional specialization may in part be a consequence of the high independence with which different features vary over time (see the 'Principle of Functional Independence' in Bartels and Zeki (2003, 2004a,b)). Complex stimulation (such as free viewing) thus leads to more distinct activation in functionally specialized areas, as each processes the features it is specialized for (Bartels and Zeki, 2004a). These considerations are of high relevance for the mapping of connectivity, as the high regional specificity of activation time courses observed during natural viewing should make correlations induced by anatomical connectivity stand out particularly well.

Thus, our approach in this study was to compare interregional correlations between pairs of regions that are known to have anatomical connections with those between nonconnected regions, both during natural viewing and rest. Even though compared to the monkey less is known about connectivity in the human brain, two sets of connections are known well enough to suit our purposes. One concerns the connections of homologous (or bilateral) areas in the two hemispheres through the corpus callosum. (Clarke and Miklossy, 1990; Pandya et al., 1971; Zeki, 1970). Reflecting these strong connections, the most consistent finding of all previous resting state connectivity studies has been strong bilateral correlations (Biswal et al., 1995; Cordes et al., 2000; Greicius et al., 2003; Hampson et al., 2002; Lowe et al., 1998; Xiong et al., 1999), which are diminished in patients with agenesis of the corpus callosum (Quigley et al., 2003). The other set of connections belongs to the language system, where anatomical studies suggest direct connections between the somewhat ill-defined regions of Broca, Wernicke, and a region in premotor cortex (Kaas and Hackett, 2000; Petrides and Pandya, 2002; Scott and Johnsrude, 2003). These are not thought to have direct connections to visual areas. This language network has also been identified using resting-state connectivity maps (Hampson et al., 2002).

We chose to combine independent component analysis and seed-based correlation maps to identify regions of interest and functional connectivity to accommodate for the strengths and weaknesses of each method, which we review under a separate subheading in the methods section.

If functional connectivity during natural viewing is indeed indicative of anatomical connectivity, and if it is so more than during rest, we would have to test the following predictions to reveal this: First, regions correlate in anatomically specific ways with other regions they are anatomically connected to. Secondly, these correlations are higher during natural viewing than during rest. And third, anatomically nonconnected regions have lower correlations during natural viewing than during rest, thus indicating a higher anatomical specificity of functional connectivity during natural viewing. We found all predictions to be true for the regions we examined in the visual as well as language-related cortex.

Methods

Our overall strategy was to identify cortical regions in the visual, auditory, and language-related cortices that were activated by natural viewing of a film, with the aim of comparing BOLD

correlations between regions that are known to be anatomically connected and between other regions. These regions were identified using spatial independent component analysis (ICA), which is ideally suited to segregate brain regions that are differentially activated during such uncontrolled conditions (Bartels and Zeki, 2004a). In most instances, ICA segregated functionally connected regions (such as left and right homologues of a given region, or a network of regions such as the language network) in separate independent component maps (ICs). Regional BOLD time courses that corresponded to the most active voxels of a given IC (e.g., voxels in left and right visual area V5) were then extracted from the original data and pairwise correlations were computed. We made our inferences on these correlations by comparing correlations between homologous and nonhomologous regions or between regions within the language network and visual regions under rest and natural viewing conditions. Details and a short review on ICA's strengths and weaknesses with respect to identifying functional connections are given below.

Stimuli and subjects

Informed consent was obtained from all subjects in accordance with the Declaration of Helsinki, and ethical approval was granted by the Ethics Committee of the National Hospital for Neurology and Neurosurgery, London, UK. Eight volunteers (five female, all right-handed, aged between 24–38) viewed the first 22 min 25 s of the James Bond movie *Tomorrow Never Dies* (including the sound track) while blood oxygen level-dependent (BOLD) activity was measured using functional magnetic resonance imaging (fMRI) (Bartels and Zeki, 2003, 2004a). Stimuli were projected onto a translucent screen of $26 \times 19°$ visual angle, which was viewed through an angled mirror. The movie was interrupted every 2.5 or 3 min with a blank period (black screen, no sound) lasting 30 s, in total eight times, and for the purposes of another study the image was switched between gray and color every 30 s, which was however barely noticed by the subjects and not relevant to this study (Bartels and Zeki, 2003).

Acquisition of fMRI data

T2*-weighted whole brain images ($3 \times 3 \times 3$ mm resolution; 48 slices, 1.8 mm thick with 1.2 mm gap, with a matrix of 64×64 pixels) were acquired in a Siemens Vision 2 T MRI scanner, using an echo planar imaging (EPI) sequence that optimized blood oxygen level-dependent (BOLD) contrast. Echo time (TE) was 40 ms. For technical reasons, results from subjects 1 to 4 were acquired using a repetition time (TR) of 4.105 s with 324 whole-brain acquisitions in 22 min 12 s, while those from subjects 5 to 8 were acquired with a TR of 3.649 s and 368 acquisitions in 22 min 23 s.

Data preprocessing

All data were preprocessed using SPM99 (Friston et al., 1995) (http://www.fil.ion.ucl.ac.uk/spm/) as follows. Whole brain images were realigned to compensate for head movement and slices were temporally realigned to compensate for acquisition time lags. Images were spatially normalized to the Montreal Neurological Institute template (approximating to the atlas of Talairach and Tournoux, 1988) and spatially smoothed with a Gaussian kernel of

6 mm full width at half maximum. In the resting state literature, it is often pointed out that BOLD signal frequencies that contribute to connectivity have less than 0.1 or 0.08 Hz (Biswal et al., 1995; Cordes et al., 2001). This is exactly what one would expect from a signal of hemodynamic origin because the physiological hemodynamic response function (HRF) acts like a low-pass filter with a cutoff around that frequency (see, e.g., Fig. 8 in Bartels and Zeki, 2004a). For this reason, data in some functional MRI studies are convolved with an artificial HRF to remove nonphysiological high-frequency noise before further analysis. ICA was applied after this stage of preprocessing. All time courses used for subsequent analysis (including BOLD signal-based correlation maps, and correlation of BOLD signals from the most active voxels of candidate regions) were band-pass filtered to suppress hemodynamic responses that were not mediated neuronally. This involved a low-pass filter, effected by convolving each time series with a canonical hemodynamic response function. The high-pass component was implemented by regressing out drift terms using a discrete cosine set. Movement-related components were removed from the BOLD signal by regression against the realignment parameters. To avoid transitional transients of movie on- and offsets that may influence rest or movie viewing-related signals, the first 15 s after each transition (referred to 'transition periods' below) was discarded. For statistical tests that directly compared natural viewing and resting state correlations (Figs. 3 and 7), the time windows considered for movie viewing were made equal to those of rest by shifting the latter forward by 30 s (length of rest). This ensured that periods of movie viewing were equivalent both in length and in position relative to the previous transition and matched those of the rest condition. We note that when the complete movie periods were considered instead, the results were virtually identical, showing that neither the relatively short duration nor the position with respect to the previous transient affected the results. For all statistical tests, correlation coefficients were Fisher Z transformed.

Independent component analysis: strengths and weaknesses in the detection of functional connectivity

ICA is a powerful method for unmixing or decomposing linear mixtures of independent sources (Bell and Sejnowski, 1995). In conventional fMRI data, spatial ICA (below simply referred to as 'ICA') has been shown to segregate task-related activity and artifacts (Bartels and Zeki, 2000a,b; Calhoun et al., 2002; Duann et al., 2002; McKeown et al., 1998; Zeki and Bartels, 1999). ICA's application to resting state data was as successful as previous correlation approaches in detecting temporally related regions (Kiviniemi et al., 2003; Van De Ven et al., 2004; Yang and Rajapakse, 2004). In the context of detecting functionally connected regions, it is however worth cataloguing the relative strengths and weaknesses of ICA compared to correlation-based approaches. Correlation maps (CMs) are based on a seed time course, whose correlation with the time courses of every voxel in the brain is mapped in a CM. The seed time course is usually taken from a voxel in the brain that needs to be selected, for example, from an anatomically or functionally defined region. This is not required with ICA. Furthermore, the specificity of CMs may be adversely affected by artefacts (induced by movement, arteries, etc.). Such artefacts are recovered into separate components and therefore removed from the components of interest by ICA. It has been theorized that another advantage of spatial ICA is

that active voxels in a given component can be temporally dependent on each other in a complete statistical sense, in comparison to the second order correlation revealed in CMs (Yang and Rajapakse, 2004). In practice, however, so far spatial ICA has not revealed networks that were not also identified using correlation alone (Van De Ven et al., 2004; Yang and Rajapakse, 2004). Furthermore, it is important to note that not all temporally dependent voxels are segregated in the same component since spatial ICA applies the independence criterion only to the spatial domain, but not to the time courses of distinct components, which may be correlated (see below). One difficulty with spatial ICA is the selection of components of interest from potentially hundreds of components delivered by ICA. Also, the choice of how many components ICA should be constrained to deliver is problematic since this may affect the degree to which ICA 'super-fractionates' correlated regions into separate components. Thus, one cannot rely on ICA to reveal the complete or in fact any functionally connected network associated to a region, while correlation maps reliably show all voxels correlated with a given seed time course (for an example, see Fig. 6, where ICs do not contain all regions that are functionally connected with the IC's most active voxel, while CMs do). This happens because spatial ICA does not impose independence constraints on the temporal variate associated to each spatially independent component. This is actually a major drawback of using ICA for the particular purpose of detecting functional connectivity, which is why we decided to combine both ICA (for the identification of functionally distinct cortical regions and potentially networks) and correlation maps (for the detection of the complete functionally connected network associated to a region of interest) in this study (see Figs. 1 and 6). The background and details of the application of spatial ICA to fMRI in general and to natural viewing data specifically are described in detail in our previous manuscript (Bartels and Zeki, 2004a). In that study, we demonstrated that spatial ICA can

successfully segregate a multitude of functionally specialized cortical and subcortical regions as well as artifacts from fMRI data collected in natural viewing conditions. ICA is successful in doing so because voxels belonging to a particular functional subdivision have highly correlated activity time courses (ATCs). In addition, during natural viewing conditions, distinct functional subdivisions have ATCs that are, if not independent, at least characteristic of each. Thus, ATCs act like a temporal fingerprint during natural conditions, allowing the segregation and identification of distinct areas reliably across different subjects (Bartels and Zeki, 2004a).

Independent component analysis: methodology

Spatial ICA was applied separately to each of the eight subjects using preprocessed data (above) as described in full detail in Bartels and Zeki (2004a). Voxels lying outside the brain were removed by manual intensity thresholding, and the data matrix [size: 324–368 (= number of whole-brain images of a given subject) × 60,000–70,000 (number of voxels)] was submitted to the 'runica' procedure supplied in the EEG package by Makeig (http://www.cnl.salk.edu/~scott/ica-download-form.html) (Makeig et al., 1997), which applied spatial ICA incorporating the natural gradient feature of Amari (1999), using the default parameters. The total number of ICs obtained in each subject was equal to the number of input images; each IC had an associated time course, which corresponded closely to the BOLD signal of the most active voxel in that IC.

Selection of ICs

Independent components (ICs) were selected by hand using anatomical heuristics. Several measures were taken to ensure that functionally relevant ICs were selected for analysis. It should be noted that inclusion of artifactual or physiologically meaningless ICs would weaken the outcome of our analysis but not bias results (or do so only towards generally lower and more similar correlations
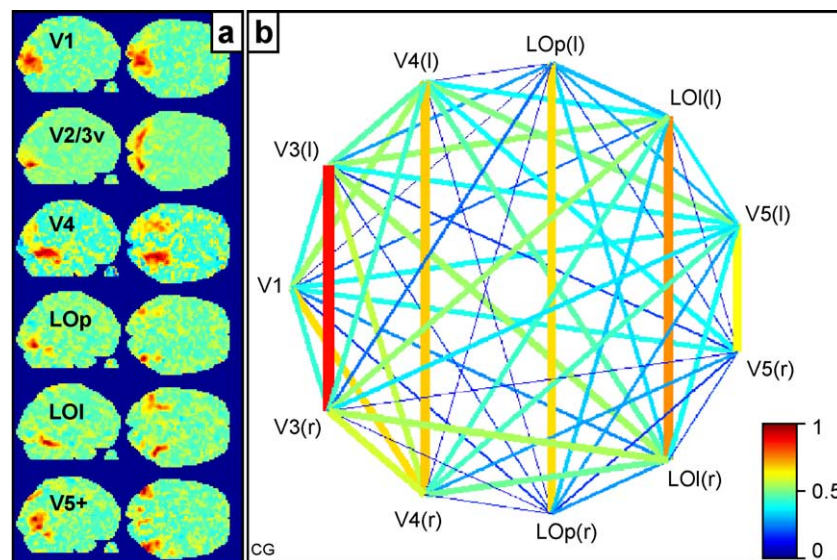

Fig. 1. Independent components (ICs) containing visual areas (a) and BOLD signal correlations between their most active voxels (b) during free viewing of a movie (shown for a single subject). (a) Glass-brain views (sagittal and transverse maximum intensity projections, no threshold applied) of occipital ICs isolated from one subject. All regions were stimulus driven and had specific and significant intersubject correlations (Bartels and Zeki, 2004a). Labels indicate the presumptive identity of the regions based on their anatomical locations. The coloring of the ICs shows the relative voxel contribution, using the same color scale shown in (b), with red indicating positive contribution, green neutral/no contribution, and blue negative contribution. (b) Correlogram visualizing the correlation (*r*) of BOLD signals between the most active voxels of areas identified in (a). Line thickness and color code indicate the correlation strength. Abbreviations: LOp: posterior part of the lateral occipital complex; LOl: lateral part of the lateral occipital complex, V5+: V5/MT and parts of ventral occipital cortex.

in all conditions). First, all functional ICs described in our previous study were also considered in this one (71 in total across all eight subjects). In short, the selection criteria were as follows: plausible anatomical location and distribution of the most active voxels, bilaterality of the most active voxels, and anatomical correspondence across subjects. In addition, an analysis of the associated activity time courses (ATCs) of the ICs revealed that ATCs of anatomically corresponding ICs of distinct subjects were correlated and that this correlation was area specific. Thus, the ICs were formally shown to contain distinct, functionally specialized and stimulus-driven areas whose anatomical location and ATC corresponded across subjects (Bartels and Zeki, 2004a). These ICs included many visual regions, the primary auditory cortex, and regions of the language-network (including Broca, Wernicke, and a premotor region) (Bartels and Zeki, 2004a). For the present study, we manually selected additional ICs that contained clusters of their most significant voxels in the occipital (visual) cortex with a bilateral distribution (some of these ICs differed across subjects and had therefore not been included in our previous analysis). While most ICs contained a bilateral pair of regions (such as left and right primary auditory cortex, see Fig. 1), some contained secondary regions (e.g., several regions of the language network in one IC, see Fig. 6). Each separate cluster of highly active voxels in an IC was treated as a separate area in subsequent BOLD signal analyses. BOLD signals were extracted from the most active voxel of each maximally active cluster in a given IC (e.g., from the two peak-voxels in left and right auditory cortex). We emphasize that ICA was used here to identify distinct cortical regions. For subsequent analyses involving ATCs, we used the BOLD signals and not the time courses associated to the ICs. This ensured that the underlying physiological signal was analyzed in the same way as in previous fMRI analyses and enabled us to measure correlations between regions even when they were isolated in the same IC (such as most bilateral regions, see Fig. 1). In total, BOLD time courses were extracted from 189 different regions (i.e., their peak-voxels) across all eight subjects.

Results and discussion

Data derived from eight subjects while viewing 22 min of the movie *Tomorrow Never Dies*, interrupted by eight resting periods of 30 s, were analyzed separately using independent component analysis (ICA), followed by correlation analyses of area-specific BOLD responses. The aim was to find out whether regions that are known to be anatomically connected have higher correlations than nonconnected regions during free viewing, as has been shown to be the case during 'resting state' (Biswal et al., 1995; Hampson et al., 2002; Quigley et al., 2003; Young et al., 2003), and to compare natural conditions with rest in that respect. For reasons mentioned in the Introduction section, we restricted our comparison to two systems whose anatomical connections are relatively well known: corresponding regions in the two hemispheres (Clarke and Miklossy, 1990; Pandya et al., 1971; Quigley et al., 2003; Zeki, 1970), and the language processing system of the cortex (Hampson et al., 2002; Kaas and Hackett, 2000; Petrides and Pandya, 2002; Scott and Johnsrude, 2003).

ICA results

Before any formal BOLD correlation analysis was made, we observed that the results obtained by the ICA dissection were

indicative of high correlations between anatomically connected areas: Most functional ICs contained bilateral pairs of clusters, indicating high and specific correlations between homologous areas in the two hemispheres (see Fig. 1). In addition, ICA sometimes isolated distinct regions in a single IC. Among these were ICs containing several or all of the speech-related regions of Broca's and Wernicke's areas and a premotor region in the dorsolateral prefrontal cortex (see Fig. 6). Like homologous regions, these are known to have strong and direct anatomical connections. Across all eight subjects, 74 and 77 regions were identified in left and right visual cortex, and 15 and 23 regions from language-related areas in left and right cortex. This amounts to an average of 24 separate regions (i.e., 12 bilateral regions) per subject, and a total of 189 extracted BOLD signal time courses across all eight subjects.

Homologous areas: selective correlations during natural conditions and rest

Most ICs in the visual cortex contained bilateral clusters, indicating strong correlations between homologous regions. As an example, we show ICs from the visual cortex of a single subject in Fig. 1a. The complete set of correlations between regions in these ICs is shown in Fig. 1b, which illustrates, in the form of a circular correlogram, the BOLD correlations between visual areas of the two hemispheres during viewing of the movie. Line thickness and color indicate the strength of the correlations. It is apparent that the strongest correlations form parallel lines that connect homologous areas of the two hemispheres. Across subjects, the correlation between bilateral or homologous areas during movie viewing was on average more than twice as high ($r_{homol.} = 0.63 \pm 0.03$ SEM) compared to correlations between nonhomologous areas ($r_{nonhomol.} = 0.30 \pm 0.02$), with a significance of $P < 10^{-7}$ (two-sample *t* test, $n = 8$ subjects). Interestingly, in the absence of stimulation, this specificity of high correlations between homologous areas as compared to nonhomologous areas was almost as high as during natural viewing ($P < 10^{-6}$) with mean correlations of $r_{homol.} = 0.59 \pm 0.02$ and $r_{nonhomol.} = 0.37 \pm 0.02$ for homologous and nonhomologous areas, respectively (see Fig. 3). In average, 19 areas per subject from the visual cortex (151 across all subjects) were considered for this analysis. Summed across all eight subjects, these formed 73 homologous pairs and 1336 nonhomologous ones. It should be noted that, in some subjects, the IC containing the calcarine sulcus (V1) showed only one central significant region, in which case it was entered as a nonbilateral area for the correlation analyses.

Fig. 2a uses a novel plot to show the correlations between visual regions during periods of film viewing, rest, and transitions in between. This plot was obtained by calculating correlations between BOLD signals of visual areas of each subject during a short window of 7 s duration, which was gliding over the complete scanning session in steps of 1 s. The resulting time series of correlation coefficients were averaged over the periods shown in an event-related fashion. To ensure precise time locking to on- and offsets and to allow for a small gliding window size, the BOLD signal was spline interpolated to 1 s steps before these calculations. This gliding–window correlation plot is suited to reveal the local correlations of both nonhomologous and homologous regions at every point in time under local stationarity assumptions. It should be noted that the values are (a) blurred as a function of the window size and (b) lower than actual values shown in Fig. 3 because

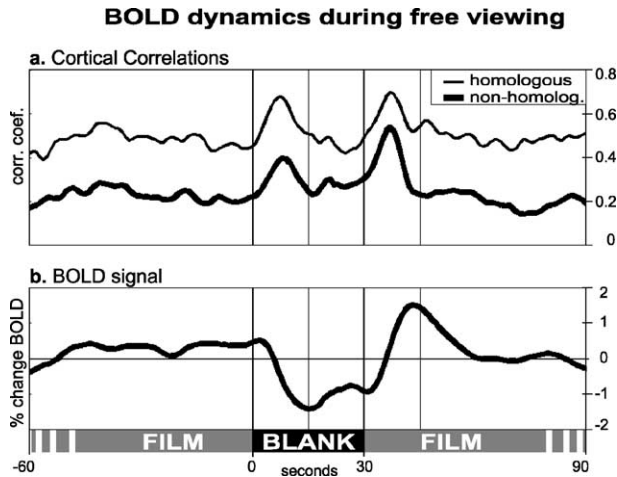## BOLD dynamics during free viewing

Fig. 2. Event-related analysis of correlation and BOLD signal change among visual areas during movie viewing and rest. (a) Mean correlation between all visual areas within subjects (in total 151 areas in all subjects), displayed separately for homologous pairs (thin line, $n = 73$ pairs summed over all subjects) and nonhomologous pairs (thick line, $n = 1336$ pairs), shown as a subject-weighted average. Correlation coefficients between pairs were calculated using a gliding window (size = 7 s) to obtain the 'instantaneous' correlation coefficient at each time point of the session. The time series of these correlation coefficients were cut up into the periods ± 1 min around the eight 30 s blank periods that interrupted the movie and averaged, first within, then across subjects. (b) Mean BOLD signal of all 151 visual areas identified by ICA in the eight subjects, time-locked ± 1 min around the blank periods and averaged (each subject with equal weight).

correlations are only calculated during the short window. Nevertheless this plot gives a semiquantitative overview over correlational dynamics in an event-related fashion. Fig. 2b shows how the average BOLD signal of all visual areas studied above varied during the periods when the movie was interrupted by the blanks, plotted in an event-related way. During film viewing, the BOLD signal was high, while the correlation among visual areas was lowest. Blank periods led to a drop of BOLD signal by about 2% and to a rise of the correlation in nonhomologous areas (see Fig. 3). Transitions from movie to blank and vice versa led to a steep rise of the correlations to about twice their normal value, interestingly regardless of whether the transition was an onset or an offset. This likely reflects nonspecific correlations across the whole brain induced by the sudden removal or introduction of audiovisual stimuli (see discussion of this phenomenon in context of Fig. 7).

While the above values demonstrate the intensity of correlations in general, Fig. 4 illustrates the high degree of anatomical specificity of interhemispheric BOLD correlations using correlation maps (CMs). These are whole-brain maps of correlation coefficients, showing each voxel's correlation with the BOLD signal of a seed voxel. In this case, the seed voxel was the most active voxel of an IC containing a visual or auditory region. Fig. 4 shows CMs derived from seed voxels taken from distinct visual regions (and auditory cortex) of one hemisphere, calculated separately for free viewing and rest (shown for a single subject). For each seed-region, its contralateral counterpart shows the highest correlation with high anatomical specificity. This, together with the ICs from a different subject shown in Fig. 1a, shows the most detailed evidence obtained so far for area-specific correlations across hemispheres during both rest and free viewing in the visual system. Seeds were taken from unilateral locations in the vicinity

of visual areas V1 (calcarine sulcus), ventral V3 (posterior lingual gyrus), V4 (medial fusiform gyrus), V5/MT (middle temporal gyrus), lateral occipital complex (LOC, lateral fusiform gyrus), and from auditory cortex (superior temporal cortex). The high similarity of CMs derived from natural viewing and rest conditions suggests that the underlying basis for the specific correlations may be quite similar in the two conditions. Neural activity originates in one case partially from imagery and spontaneous activity of other sorts (Leopold et al., 2003) and in the other from external stimuli. In both situations, the strong interhemispheric connections between homologous areas as well as their identical function are likely to form the basis of the specificity of these correlations (Biswal et al., 1995; Clarke and Miklossy, 1990; Cordes et al., 2000; Lowe et al., 1998; Pandya et al., 1971; Quigley et al., 2003; Zeki, 1970).

One of our hypotheses is that natural viewing of a movie provides a sufficiently high degree of complexity and variability to avoid any bias of correlations in favor of this or that direction and thus is indicative of anatomical connectivity in the brain. If the variability of the movie was insufficient (and thus led to biases in interregional correlations), one would expect that different movies would lead to different correlation maps. We tested this by calculating separate CMs for the first and second halves of the movie, which provide two independent data sets of natural viewing. Fig. 5 shows, using the example of V5 and the primary auditory cortex of a single subject, that CMs calculated for different parts of the movie are virtually indistinguishable. This is consistent with our previous finding that the mapping of functional preferences for color, faces, human bodies, and language led to the

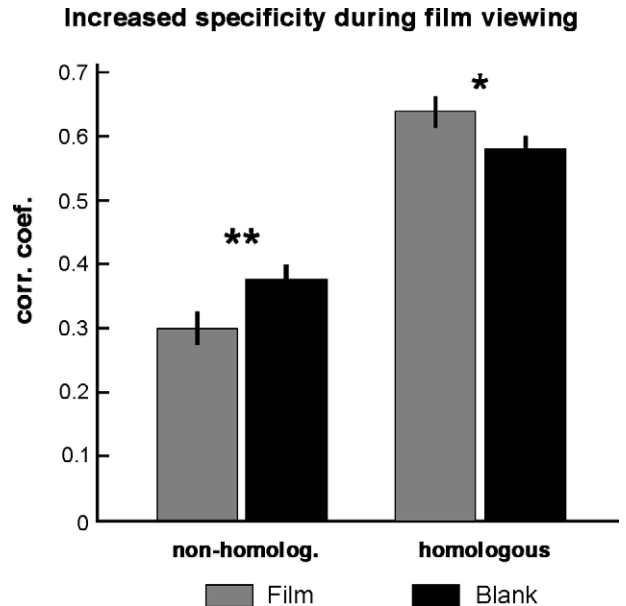## Increased specificity during film viewing

Fig. 3. Correlations between homologous and nonhomologous visual areas during natural viewing and rest. Shown are the mean correlation coefficients (subject weighted; $\pm$SEM, $n = 8$) of homologous ($n = 73$) and nonhomologous ($n = 1336$) pairs of areas averaged across all eight subjects (151 visual areas in total). Nonhomologous areas decorrelated during movie viewing (paired t test: $P < 0.003$, $n = 8$ subjects) compared to blank periods, while homologous areas increased their correlations during movie viewing ($P < 0.03$). Homologous regions had higher correlations than nonhomologous ones during both movie viewing and rest (two-sample t test: $P < 10^{-6}$, $n_1 = 8$, $n_2 = 8$). A two-way ANOVA revealed a significant interaction between stimulation and homology of regions ($P < 0.008$).
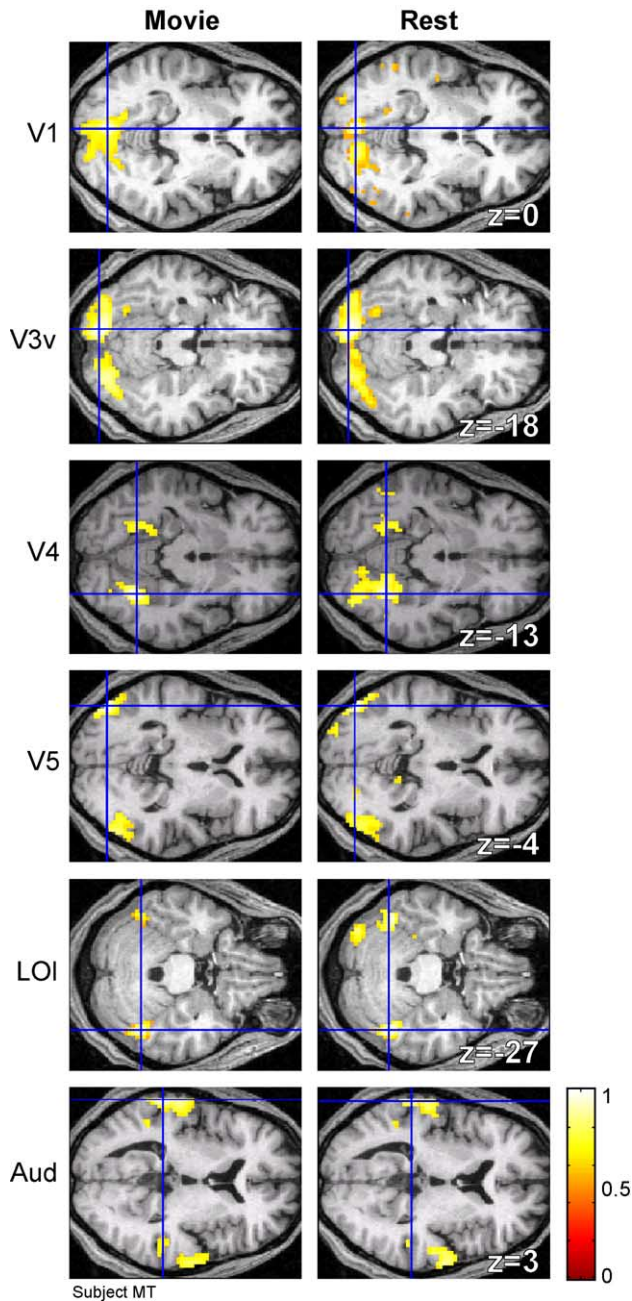
Fig. 4. Correlation maps (CMs) reveal highly specific interhemispheric correlations for visual and auditory areas during movie viewing (left) and rest (right). CMs show the correlation of every voxel in the brain of a single subject with the activity time course of a given seed voxel. Seed voxels were taken from the most active voxel of the distinct ICs that contained a distinct visual or auditory region (marked by the orthogonal blue lines in each section). Regions were labeled according to their putative identity: primary visual cortex (V1), ventral V3 (V3v), medial fusiform gyrus (V4), medial temporal cortex (V5), the lateral aspect of the lateral occipital complex (LOl), and primary auditory cortex (Aud). CMs were thresholded at $r = 0.6$ and superimposed on transverse sections through the individuals' anatomical scan. The color code indicates the correlation coefficient (r).

same results, no matter whether first or second halves of the movie were considered (Bartels and Zeki, 2003). It is reasonable to assume that viewing a movie will mainly reveal interregional correlations associated to regions involved in this task, such as

visual and auditory ones. Functional connectivity of, for example, motor regions is likely to be less selective and less detectable in this situation simply because they were not specifically activated. One may however still expect to find some residual neuronally specific correlations even in noninvolved regions, comparable to those found under rest conditions, as is suggested by findings of Arfanakis et al. (2000).

Visual areas: decorrelation and increased specificity during natural viewing

In addition to this difference between homologous and nonhomologous pairs of regions, we found another, maybe more surprising effect: Distinct visual areas decorrelated during viewing of the movie compared to rest, with the exception of connected, homologous areas, which increased their correlation. Nonhomologous areas had a correlation of $r = 0.30 \pm 0.02$ SEM during film viewing, which increased by nearly a third to $r = 0.37 \pm 0.02$ during rest, with a significance of $P < 0.003$ (t test across subjects, $n = 8$) or of $P < 10^{-20}$ (across all pairs of areas, $n = 1336$) (see Fig. 3). Decorrelations between visual areas during natural processing are also consistent with our previous observation that more regions engage in more differential processing during exposure to natural stimuli compared to conventional epoch-style stimuli (Bartels and Zeki, 2004a). Natural stimuli seem to elicit the functional specificity of each area in a more prominent way than rest or specialized stimuli, as each area engages in its distinct and specialized processing. This is what one would expect with complex stimulation, given the presence of a multitude of functionally specialized areas. In contrast, homologous areas, which have strong interhemispheric connections, increased their correlations during natural viewing compared to rest, from $r = 0.585 \pm 0.02$ SEM during rest to $r = 0.634 \pm 0.03$ during film viewing, with significances of $P < 0.03$ ($n = 8$ subjects) and $P < 0.005$ ($n = 73$ pairs of areas). This is not a large change in correlations. However, together these changes in correlations reveal a clear double-dissociation between homologous (strongly connected anatomically) and nonhomologous (not consistently connected) regions during natural viewing and rest, indicative of an interaction between stimulus and connectivity. We tested the significance of this interaction using a two-way ANOVA, with the two factors being anatomical connectivity (i.e., homologous or not) and stimulation (i.e., rest or film), in which all correlation coefficients of the four combinations were entered. The interaction term (connectivity $\times$ stimulation) was highly significant (with $P < 0.008$ for one value per subject per group; and $P < 0.002$ for one value for every pair of areas per group), demonstrating that blank and film had opposing effects on correlation coefficients, depending on the connectivity of the areas. Since homologous areas not only have strong anatomical connections but also have the same functional specialization and a similar vascularization, the changes in correlations cannot be attributed solely to the anatomical connections. Furthermore, specific connections between several of the nonhomologous visual regions will have affected (and potentially weakened) the above observation of an interaction between stimulus and connectivity. It was thus important to repeat the above analysis for regions that are located within a single hemisphere, and which can be divided into pairs for which anatomical connections are well established, and other pairs that are thought not to have direct anatomical connections.
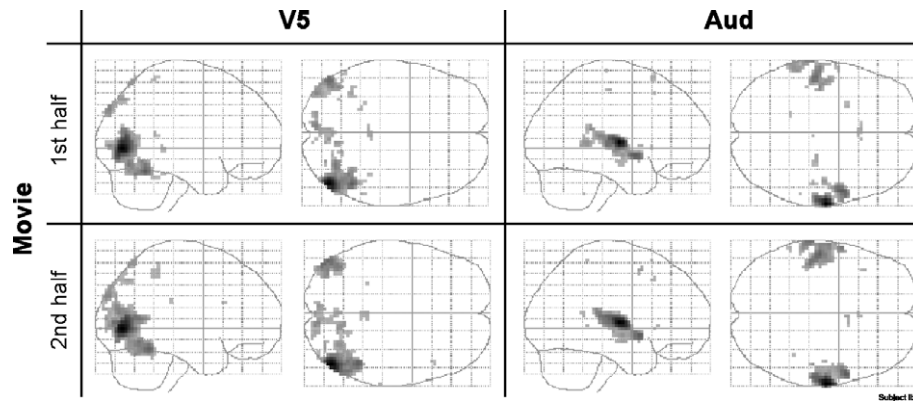
Fig. 5. Correlation maps (CMs) calculated separately for first and second halves of the movie. Shown are CMs of presumptive visual area V5/MT (seed in right V5) and primary auditory cortex (Aud; seed in right hemisphere) of a single subject, displayed as glass-brain projections. CMs were thresholded at $r = 0.4$.

Language network and visual regions: correlations between anatomically connected and nonconnected regions

We wanted to confirm the above observations for sets of areas located within a single hemisphere for which the existence or nonexistence of direct anatomical connections are known. Despite the limited knowledge of anatomical connectivity in the human, the network of areas involved in language processing seemed adequate for the set of 'connected' areas. Correlations within this network could be compared to those between its constituent regions and visual regions for the set of 'nonconnected' areas. Detailed anatomical studies suggest that Broca's area, Wernicke's area and a premotor region in the dorsolateral prefrontal cortex have direct anatomical connections (Kaas and Hackett, 2000; Petrides and Pandya, 2002; Scott and Johnsrude, 2003), while we are not aware of direct anatomical connections between these regions and the visual regions included in our analysis. Consistent with this, Hampson et al. (2002) showed correlations during rest that were specific to the language network. We note that the terms Broca's and Wernicke's area do not do justice to the complex functional and anatomical organization of the general regions depicted by these terms, and we use them here to indicate in broad terms the anatomical regions consistently activated in language tasks (Blank et al., 2002; Scott and Johnsrude, 2003; Wise et al., 2001).

Our ICA results provided a first indicator for specific correlations between the three regions. In our previous study of a time-based dissection of the human cortex, we had identified among other functional subdivisions one (contained in a separate IC) that represented putative Wernicke's area (BA 22). The activation time courses associated to Wernicke-ICs in different subjects were significantly correlated, and this correlation was specific to Wernicke-ICs, thus showing its specific functional involvement that was preserved across subjects (Bartels and Zeki, 2004a). Interestingly, we found that most Wernicke ICs also contained one or two additional clusters of voxels whose location corresponded to Broca's area and/or to the premotor region (BA 6) (see Fig. 6 top). In order to establish the full functional network associated to Wernicke's area, we calculated correlation maps (CMs) based on the most active voxel in each subject's Wernicke-IC during movie viewing. As expected from the ICs, the CMs consistently revealed clusters in Broca's area and in the premotor region (BA 6), as shown in Fig. 6 (bottom) using data derived from three subjects. Note that CMs revealed the functional network in

full, while some ICs lacked one of the functionally connected regions, which may have been isolated in another temporally correlated IC (see Methods section). Across all subjects, we identified 38 language regions (including Wernicke's, Broca's, and the premotor region) in 13 hemispheres. The natural viewing ICs and CMs corresponded closely to those of Hampson et al. (2002), who obtained similar CMs during rest.

Highest specificity of correlations during natural viewing

Finally, we wanted to find out whether these correlations were more specific during natural viewing compared to rest, which would confirm our results obtained in the visual system, but for the more stringent case of within-hemisphere correlations of areas with known—present or absent—anatomical connectivity. We therefore compared the correlations between the three connected regions of Broca's, Wernicke's, and the premotor area (within-hemispheric pairs only, 37 in total) on the one hand, with correlations of these language areas with the visual ones ('nonconnected,' only within-hemispheric pairs, 379 in total) on the other hand, both during free viewing and rest. The results were even more clear-cut than those obtained above for homologous versus nonhomologous visual areas (see Fig. 7): Anatomically connected regions increased their correlations during natural viewing ($r = 0.44 \pm 0.06$ SEM) compared to rest ($r = 0.26 \pm 0.07$) (paired t test: $P < 0.01$, $n = 13$ hemispheres, and $P < 0.004$ for $n = 37$ area pairs), while nonconnected areas decorrelated during natural viewing ($r = 0.02 \pm 0.04$) compared to rest ($r = 0.05 \pm 0.03$). The latter relation was significant only for area-weighted statistics ($P < 0.003$, $n = 379$ pairs) and not for hemisphere-weighted statistics ($P < 0.23$, $n = 13$). The interaction between connectivity and stimulation was tested using a two-way ANOVA, which turned out near significant with $P < 0.06$ for hemisphere-weighted values, and significant with $P < 0.006$ for area weighted values. We also show the correlations during transition periods for connected (0.34 ± 0.06 SEM) and nonconnected (0.12 ± 0.05) regions to demonstrate that transients induced by stimulus on- and offsets lead to the least specific correlations: Even nonconnected regions showed significant correlations during transitions, which were higher than those observed during rest or film ($P < 0.02$, the former reaching significance only for area-weighted statistics with $P < 0.001$). These transitional correlations merely reflect the general and
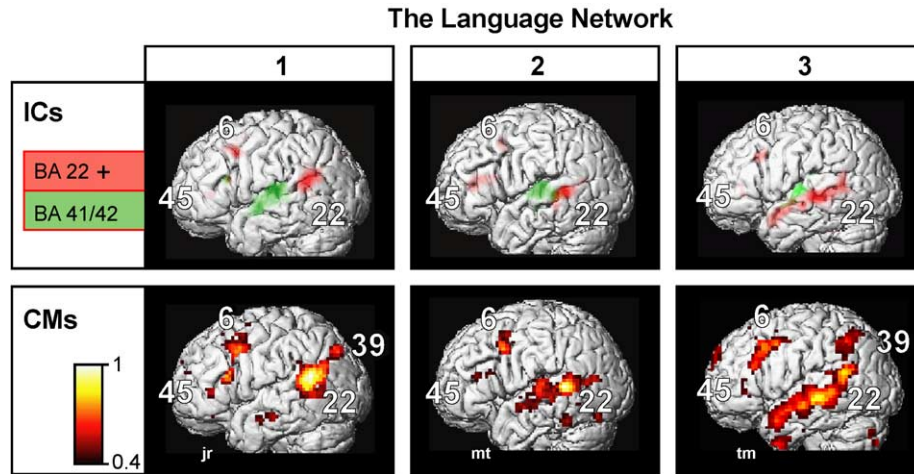
Fig. 6. Independent components (ICs) and correlation maps (CMs) revealing the putative network of areas involved in language processing shown on the example of three subjects (1–3). Top row: structural brains of individual subjects, with two separate ICs superimposed (thresholded at 30%). The IC shown in green contains the primary auditory cortex (BA 41/42) and the one in red Wernicke's area (BA 22) with secondary clusters in Broca's area (BA 45) and in the premotor cortex (BA 6). Bottom row: CMs (of BOLD signal) calculated for the seed of the most active voxel of Wernicke's area (based on the IC) for periods of film viewing, thresholded at $r = 0.4$. Note the consistent involvement of Broca's area (BA 45) and a premotor region (BA 6) in both ICs and CMs. Also note that the ICs do not reveal the complete connectivity map revealed by the CMs. The color scale cannot be taken at face value since activity buried in sulci is displayed with reduced intensity.

simultaneous increase or decrease of activity across large parts of cortex associated to on- and offsets of stimulation and are entirely distinct from the more specific correlations during film viewing and even from those during rest. These unspecific correlations induced by on/off transitions were also present within the visual cortex as is evident in the time-resolved correlation plot of Fig. 2a that shows a steep rise of correlations after transitions. This observation should be taken as a caveat for traditional epoch studies. If such studies are later analyzed in view of inferring functional or effective connectivity, an optimal design would avoid sharp on/off transitions (such occur when blank epochs are alternated with experimental epochs), use longer epochs and exclude transitional periods from the analysis (as was done here), or explicitly account for the transients in the model used.

We conclude from these findings that while both natural viewing and rest are conditions that lend themselves for the derivation of neuronally specific connectivity maps, those obtained during natural conditions are significantly more specific and also considerably more sensitive.

Final remarks and conclusion

We have examined our empirically inspired hypothesis that functional connectivity (i.e., interregional correlations) observed under natural conditions may be indicative of anatomical connectivity. Our results show that regions known to have anatomical connections have high and specific correlations. In particular, we revealed the most specific functional connectivity shown to date between homologous pairs of visual areas and also demonstrated correlations between regions of the language network during natural conditions that reflect their anatomical connectivity with high specificity. A comparison of interregional correlations during natural viewing and rest revealed that natural viewing provided correlations that were more specific to anatomically connected regions, and also that these correlations were considerably stronger compared to those obtained during rest. We demonstrated a double

dissociation between anatomically connected and nonconnected regions during natural viewing and rest, in that connected regions increased their correlations during natural viewing compared to rest while nonconnected areas decreased theirs. Our results lead us to suggest that correlation maps obtained during natural conditions are suitable to reveal anatomical connectivity and that they are more sensitive and more specific in doing so than those obtained during rest.

The most likely explanation for this lies in the enhanced signal-to-noise ratio during natural conditions compared to rest.
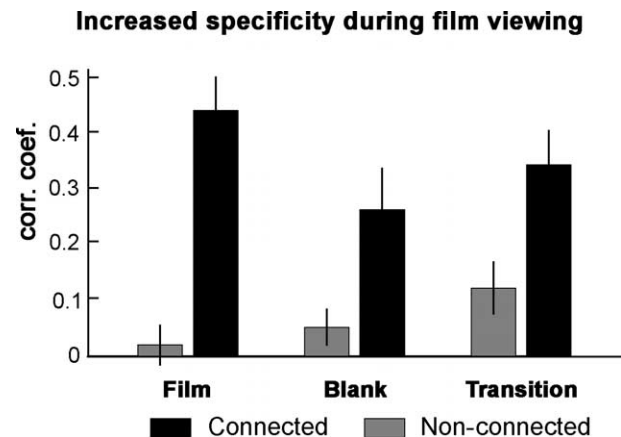

Fig. 7. Effects of film viewing, rest, and transition periods on BOLD correlations between anatomically connected (within the language network) and nonconnected regions (between visual regions and language network). Correlations within the language network increased during natural viewing, while correlations between language and visual regions decreased. The language network included Wernicke's area (BA 22), Broca's area (BA 45), and the premotor region (BA 6), $n = 38$ regions in 13 hemispheres. Correlations between nonconnected regions were obtained by correlating visual areas (of Fig. 3) with areas of the language network. All correlations were calculated for within-hemispheric pairs of areas, error bars indicate ± SEM ($n = 13$).

The BOLD signal is considerably lower during rest, with spontaneous neural activity (Leopold et al., 2003), unspecific blood flow changes, and mental imagery being the likely contributors to the signal. We hypothesize that natural conditions lead to equally unbiased brain dynamics that is suitable to reveal anatomical connectivity but at an enhanced signal intensity variation compared to the noisy background. The high complexity and dynamic variability in natural conditions are a crucial factor in this. As we have shown in our previous study, natural conditions activate more regions with a higher specificity than conventional stimuli (Bartels and Zeki, 2004a). The highly region-specific activity is thus likely to allow correlations induced by direct anatomical connections stand out. Our previous study showed that entirely distinct parts of the movie led to virtually indistinguishable yet functionally specific activity patterns (Bartels and Zeki, 2003). We replicate this finding here for correlation maps calculated for separate parts of the movie, revealing that functional connectivity was also preserved. Thus, movies appear to provide a good approximation to the rich dynamic complexity inherent to natural conditions without being strongly biased by the precise movie chosen or its length.

Despite this and as pointed out in the introduction, we note that inferring anatomical or effective connectivity from functional data will always remain inferential. By definition, functional measurements do not reveal anatomical properties or causal relationships, especially not if based on BOLD signal whose physiological origins we are just beginning to understand (Logothetis et al., 2001). The same criticism applies to the inference of effective connectivity, which assigns weights to the directional causal influence one area is thought to exert upon another in the context of tasks or other factors. In addition to the above caveat, the sophisticated tools required for inference of effective connectivity depend heavily on (invariably simplified) anatomical models (Buchel and Friston, 1997; Friston and Buchel, 2000; Friston et al., 2003). Despite this, the inference of effective connectivity has provided interesting neurobiological insights, and we are confident that the noninvasive inference of anatomical connectivity based on the methods described here will be equally valuable in complementing other tools, evidence, or theories in neurobiology. Even though functionally derived connectivity can never be taken as proof, but rather as an indicator of anatomical connectivity, it can always be taken as a sign of commonality—whether this is anatomical connectivity, similar function, or common input—or, in most cases, all three.

Noninvasive tools for the mapping of anatomical connections—or developing hypotheses about these—are of high value especially in the human. One anatomical alternative is diffusion tensor imaging (DTI), which allows the tracing of fiber tracks along the preferred diffusion preference of water along myelinated fiber bundles (Parker et al., 2002). While this method delivers impressive results, it is mostly limited to connections that originate in subcortical nuclei or white matter. The numerous fiber crossings near the cortex are difficult to resolve within the dimensions of DTI-weighted image voxels and thus make corticocortical tracing difficult, even though better solutions are in sight (Tuch et al., 2003). We therefore envisage that DTI and connectivity patterns inferred on the basis of natural conditions may be ideally suited to complement each other for the charting of corticocortical anatomical connectivity in vivo.

In conclusion, our results are compatible with our view that the structural and functional organization of the cerebral cortex is revealed most acutely during complex, more natural conditions. Cortical regions showed relatively low temporal correlations during exposure to natural conditions, with the exception of anatomically connected regions, which had high and anatomically specific correlations. Functional connectivity as measured during natural viewing may therefore be a useful indicator for anatomical connectivity in vivo.

Acknowledgments

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