Interspecies activity correlations reveal functional correspondence between monkey and human brain areas

Dante Mantini[1–3], Uri Hasson[4,5], Viviana Betti[2,3], Mauro G Perrucci[2,3], Gian Luca Romani[2,3], Maurizio Corbetta[2,3,6,7], Guy A Orban[1,8] & Wim Vanduffel[1,9,10]

Evolution-driven functional changes in the primate brain are typically assessed by aligning monkey and human activation maps using cortical surface expansion models. These models use putative homologous areas as registration landmarks, assuming they are functionally correspondent. For cases in which functional changes have occurred in an area, this assumption prohibits to reveal whether other areas may have assumed lost functions. Here we describe a method to examine functional correspondences across species. Without making spatial assumptions, we assessed similarities in sensory-driven functional magnetic resonance imaging responses between monkey (*Macaca mulatta*) and human brain areas by temporal correlation. Using natural vision data, we revealed regions for which functional processing has shifted to topologically divergent locations during evolution. We conclude that substantial evolution-driven functional reorganizations have occurred, not always consistent with cortical expansion processes. This framework for evaluating changes in functional architecture is crucial to building more accurate evolutionary models.

A basic challenge in comparative neuroscience is to develop comprehensive models explaining evolution-driven changes in brain function between primate species. Functional magnetic resonance imaging (fMRI) is currently the technique of choice for comparative sensory and cognitive experiments in monkeys and humans[1–3]. Interpretation of comparative fMRI often relies on spatial assumptions related to cortical expansion during evolution[4]. For example, cortical surface expansion models use putative homologous areas as corresponding landmarks in monkeys and humans to align the fMRI activation maps and to identify interspecies functional similarities across the cortex[5]. However, the premise that homologous areas are both anatomically and functionally equivalent is not always valid. A few comparative fMRI studies have indeed shown that particular functions in an area of one species are lacking in the presumed homologous area of the other species[3,6]: they may be either lost or shifted to areas that do not anatomically or topographically correspond[7]. Recent evolutionary theories have even suggested that functional reorganization in the brain may be independent of cortical expansion[8,9]. In cases where evolutionary changes in function are reported for an area, the constraints inherent to cortical surface expansion models will impede identification of whether (and which) other areas carry out the displaced functions. Thus, one needs complementary approaches that assess functional correspondence (analogies) without imposing topological constraints. To address this problem, we developed a method to identify analogies across species by measuring the temporal correlation between sensory-driven fMRI responses.

Here we applied the interspecies activity correlation (ISAC) method to natural vision data collected in monkeys and humans. After validating the seed-based ISAC method in selected visual areas for which homology and analogy are well accepted, we examined other areas that go beyond the boundaries of current knowledge. Finally, we tested for interspecies activity correlation across all the areas that were activated by the test movie in our human and monkey subjects. The ISAC method will prove crucial for defining cortical regions that correspond functionally but not anatomically and for improving existing evolutionary models.

RESULTS

Description of the ISAC method

The ISAC method neither relies on information about stimulation protocols nor on prior knowledge about corresponding non-human and human brain areas. It requires specific preprocessing techniques and statistical analyses to detect similar activity profiles between different species, under the accepted assumption that fMRI activity in a given brain area reflects a specific type of functional processing. As it compares evoked responses to the same task or sensory stimulation, the data need to be collected in the different species under the same experimental protocol, particularly with regard to the order and timing of the events.


Figure 1 | Detection of activity correlations between monkeys and humans. (**a–d**) Similarities in the fMRI time courses across species were assessed by temporal correlation, which may be above (solid lines) or below a given statistical threshold (dashed lines). Different regions of interest (ROIs) are indicated by arbitrary colors, and linked graphs show putative brain activity time courses. Intraspecies activity correlation was measured by comparing the time course of a selected area with the voxel time courses in the same brain (**a**). Interspecies activity correlation was measured by comparing the time courses of a monkey (**b**) and human (**c**) area with the voxel time courses in the other species. Interspecies activity correlations between time courses in multiple monkey and human brain areas (**d**).

Following general preprocessing steps and conversion of the functional volumes into standard coordinate systems, we convolved the fMRI data with a canonical hemodynamic response function from the other species to account for differences in hemodynamic response function between species (Online Methods, **Supplementary Figs. 1** and **2** and **Supplementary Note**). Next, we removed nonneuronal signal components measured in the white matter and cerebrospinal fluid from the data by linear regression. We similarly removed nonselective signal components present across multiple brain areas[10] to increase the sensitivity during subsequent analysis steps. We averaged multiple datasets of subjects from the same species to preserve the stimulus-evoked signals within a species while reducing spontaneous, stimulus-independent activity (Online Methods).

To assess the functional similarities of brain areas in the two species, we calculated the temporal correlations between their stimulus-related responses. We first correlated the average time course of a specific seed region of interest with the time courses from all conspecific voxels to examine functional relationships with other regions in the same species[11] (**Fig. 1a**). Subsequently, we correlated the time course of the same seed region of interest with those from all non-conspecific voxels (**Fig. 1b,c**). Finally, we assessed large-scale functional similarities of multiple cortical regions showing stimulus-evoked responses. In particular, we calculated correlations between average time courses of all activated areas in the two species to create an ISAC matrix (**Fig. 1d**). In all analyses, we corrected statistics for autocorrelation in the fMRI time series and for multiple comparisons (Online Methods and **Supplementary Fig. 3**).

Applying the ISAC method on natural vision data
We validated the ISAC method using natural-vision fMRI data collected in four monkeys and 24 humans. We sought to avoid any task-paradigm modeling and to examine interspecies functional similarities across multiple brain regions in a manner that would have been challenging with experimentally controlled stimulation paradigms. Indeed, natural vision conditions evoke activity in large portions of the cortex and minimize correlations between responses to different stimuli[10,12]. We acquired monkey and human fMRI data with cerebral blood volume–weighted and blood oxygen level–dependent techniques, respectively. All participants freely watched and listened (through headphones) to 30 min of the film *The Good, the Bad and the Ugly* by Sergio Leone. We presented the movie clips six times to monkeys and once to humans. We monitored eye movement during scanning. The related data showed significantly greater variability in the eye traces of humans ($t = 2.32$, $P = 0.028$) compared to monkeys (**Supplementary Fig. 4a**), likely owing to the extensive passive fixation training that the animals received before the current
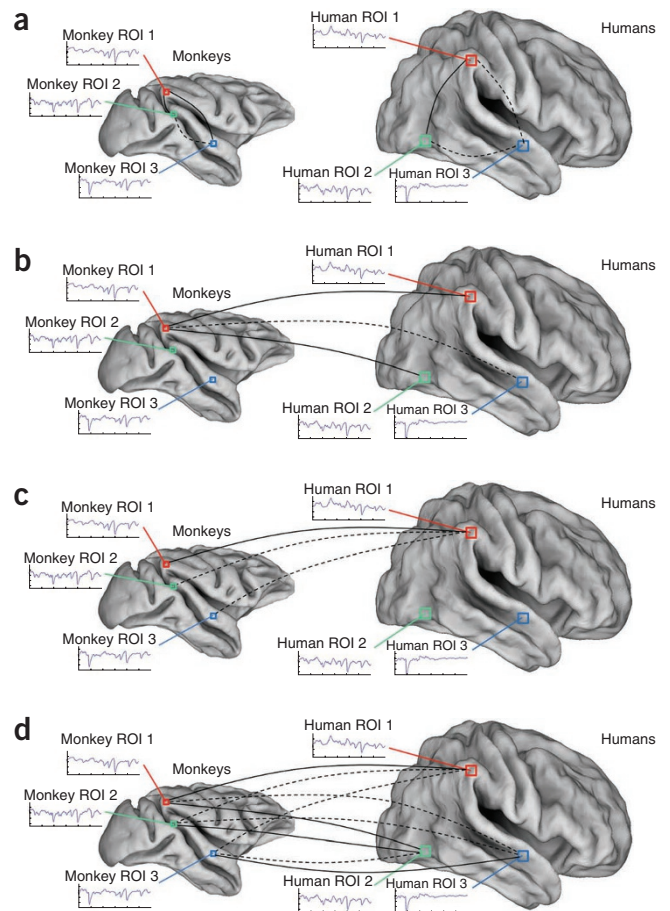
experiment. However, eye-movement signals were significantly correlated ($P < 0.001$) across monkeys ($r = 0.36$), across humans ($r = 0.25$) and between species ($r = 0.22$, **Supplementary Fig. 4b**), in line with previous reports[13].

To detect brain regions with consistent stimulus-evoked fMRI activity, we first calculated intersubject correlation maps[10] (false discovery rate (FDR) of $q < 0.05$) for each of the two species (Online Methods). We found correlations in 30.5% and 29.8% of the monkey and human cortical surfaces, respectively (**Fig. 2**). In humans, the spatial maps encompassed visual, parietal and temporal areas, mostly those involved in lower and higher-level visual and auditory processing (**Fig. 2a**). In monkeys, striate and extrastriate visual cortex contributed much more to the correlation pattern than did auditory and parietal cortex (**Fig. 2b**). In contrast to our observations with humans, we observed prefrontal areas in the intersubject correlation map of macaque monkeys. The observed differences between monkey and human intersubject correlation maps largely matched results from previous comparative fMRI studies[4,6,14]. Definition of brain regions with consistent stimulus-evoked fMRI activity was critical for the selection of seed areas to be used in ISAC analyses.

Functional correspondence in early visual areas
We first applied our ISAC analysis to the dorsal and ventral subdivisions of visual areas V1 and V2 (V1d, V1v, V2d and V2v), for which anatomical and functional correspondences between monkey and human counterparts are well accepted[15]. We observed high and significant correlations ($r \geq 0.58$, $P < 0.001$) between the

Figure 2 | Intersubject correlation of brain activity during natural vision. (**a,b**) Spatial maps of correlated brain activity (FDR of $q < 0.05$) across 24 human volunteers (**a**) and across 4 monkeys (**b**), plotted on a respective flattened cortex. Correlations are expressed in r values. Boundaries of identified areas are superimposed onto the cortex. Approximate locations of parietal, auditory and frontal regions is indicated by green, purple and white dashed lines, respectively. Labels 2, 3b, 5L, 6, 7a, 7A, 7P, 7PC, 9, 44, 45 and 46 indicate Brodmann areas (and subregions). Labels TE1.0, TE1.1, TE1.2, TE3, PFcm, PFt and PGp indicate von Economo areas (Online Methods). Other areas not defined in the text are: AITd, dorsal anterior inferotemporal; DP, dorsal prelunate; FEF, frontal eye fields; FFA, fusiform face; FST, fundal superior temporal; IFG, inferior frontal gyrus; KO, kinetic occipital; LOC, lateral occipital complex; MIP, medial intraparietal; MSTd, dorsal medial superior temporal; MSTl, lateral medial superior temporal; OFA, occipital face area; PIP, posterior intraparietal; PO, parieto-occipital; PPA, parahippocampal place area; SII, secondary somatosensory area; STPa, anterior superior temporal polysensory area; V3d and V3v, visual area V3 dorsal and ventral subdivisions; V4t, transitional visual area V4; V7 and V8, visual areas V7 and V8; VIP, ventral intraparietal; VOT, ventral occipitotemporal; VP, ventroposterior visual.
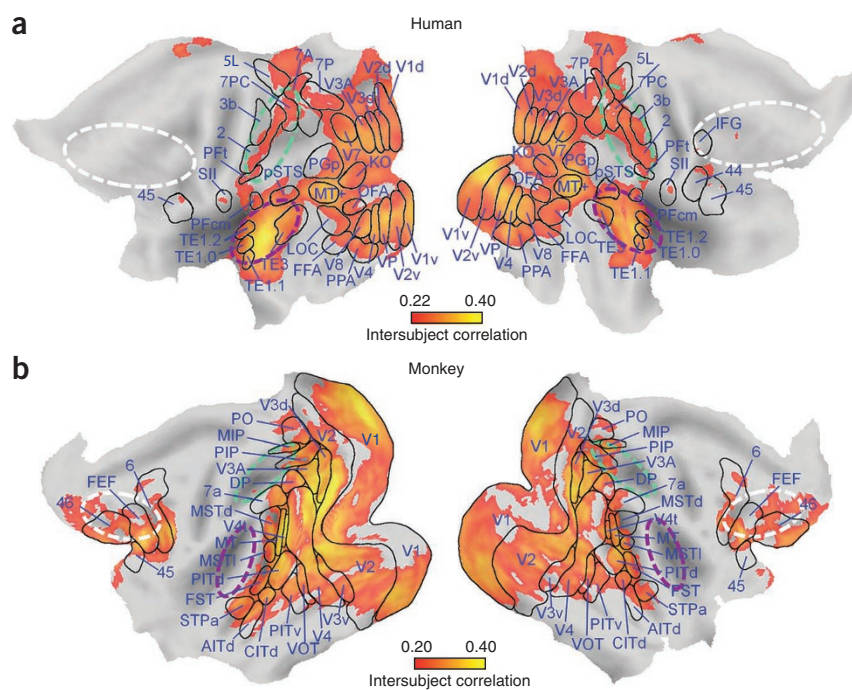
corresponding areas of the two species (**Supplementary Table 1**). However, such correlations can be induced partially by nonselective, stimulus-related components common to many areas[10,12]. To minimize contributions by nonselective components, we extracted a common, stimulus-related response for each species by averaging the fMRI signals from all voxels in the intersubject activity correlation map (**Fig. 2**). The nonselective components correlated significantly between monkeys and humans ($r = 0.56$, $P < 0.001$) and we removed them from the data by linear regression. This additional step reduced the intraspecies activity correlations, yet increased the specificity of the ISAC procedure (**Supplementary Figs. 5** and **6**). When we repeated the ISAC analysis on the early visual areas, we found reduced, though still significant, interspecies correlations ($r \geq 0.37$, $P < 0.001$) (**Supplementary Table 1**).

As the monkeys viewed the movie multiple times, we tested the robustness of the results across movie repetitions. We measured interspecies activity correlation using the entire human dataset and subsets of monkey data corresponding to single repetitions (**Supplementary Table 1**). All correlation values were still significant ($r \geq 0.30$, $P \leq 0.001$), and we observed no differences across movie repetitions (one-way Kruskal-Wallis analysis of variance, $\chi^2 = 8.11$, $P = 0.150$). This suggests that habituation effects in the monkeys, if present, affected the ISAC results only minimally.

As it is well established that cortical functions depend on networks rather than individual areas, we attempted to detect correspondence between functional networks across species by using the seed-based ISAC mapping. We first selected early human visual areas as seeds, and we examined the resulting intraspecies and interspecies activity-correlation maps (**Fig. 1a,c**). For all seeds, we observed an intraspecies correlation pattern that clearly extended over a large network of visual areas. This generally resulted in the detection of more than one functionally related visual area in the other species. By seeding in right human V1d area, we

obtained a strong ISAC focus in right and left monkey V1d areas (**Supplementary Fig. 7**). Other early visual regions of the human correlated with anatomically correspondent areas of the monkey.

Functional correspondence in the middle temporal region

The monkey middle temporal (MT or V5) region is an extrastriate visual area for which strong anatomical and functional evidence exists that it is homologous to human MT (or V5) region, the largest component of the human MT complex (MT+). Using ISAC mapping we visualized all conspecific and non-conspecific voxels with activity similar to that in the bilateral monkey MT region[16] (**Fig. 1a,b**). To assess the reproducibility of the ISAC mapping, we extracted seed time courses either from monkeys 1 and 2 or from monkeys 3 and 4, and we calculated the intra- and interspecies correlations in the complete monkey and human datasets, respectively (**Supplementary Fig. 8a,b**). For both selections, we found the predicted functional correspondence between monkey MT and human MT+ regions both selections with high reliability (spatial correlation between maps, $r = 0.818$, $P < 0.001$). As the MT region is typically activated together with other motion-sensitive areas, we obtained an interspecies activity correlation pattern that included not only the MT+ area but also a network of areas comprising visual areas V3, V3A and V4 in humans. The same analysis using human MT+ as the seed region of interest also revealed its monkey counterpart in a reliable manner (spatial correlation between maps, $r = 0.797$, $P < 0.001$) (**Supplementary Fig. 8c,d**). Thus, in addition to early visual regions, we also demonstrated convergence between anatomical and functional correspondence in extrastriate visual areas such as the MT region.

Does anatomical correspondence imply analogy?

Recent evolutionary theories have suggested that functional reorganization does not always adhere to cortical surface expansion
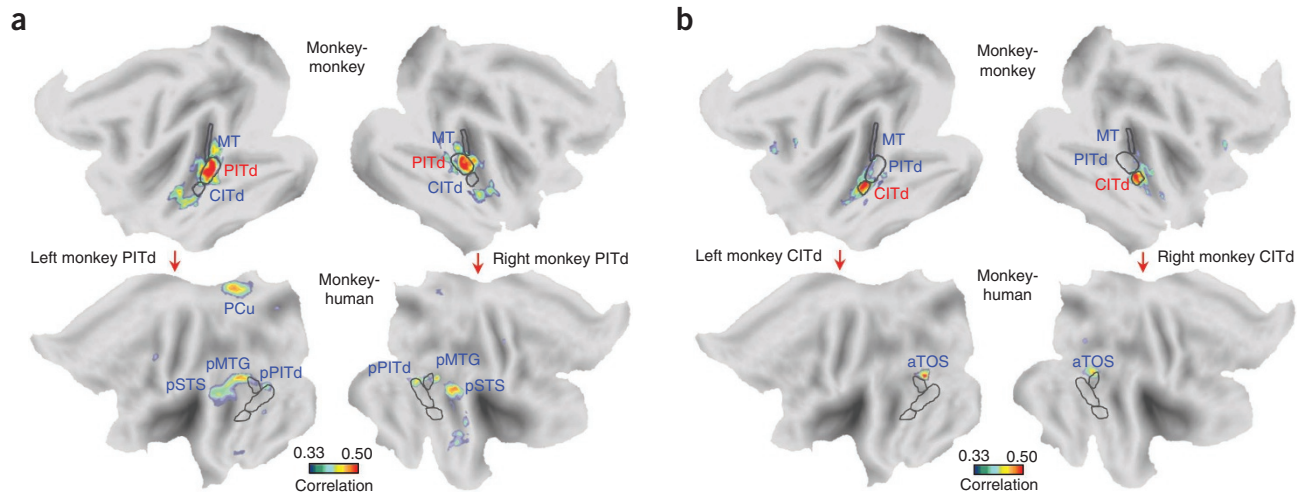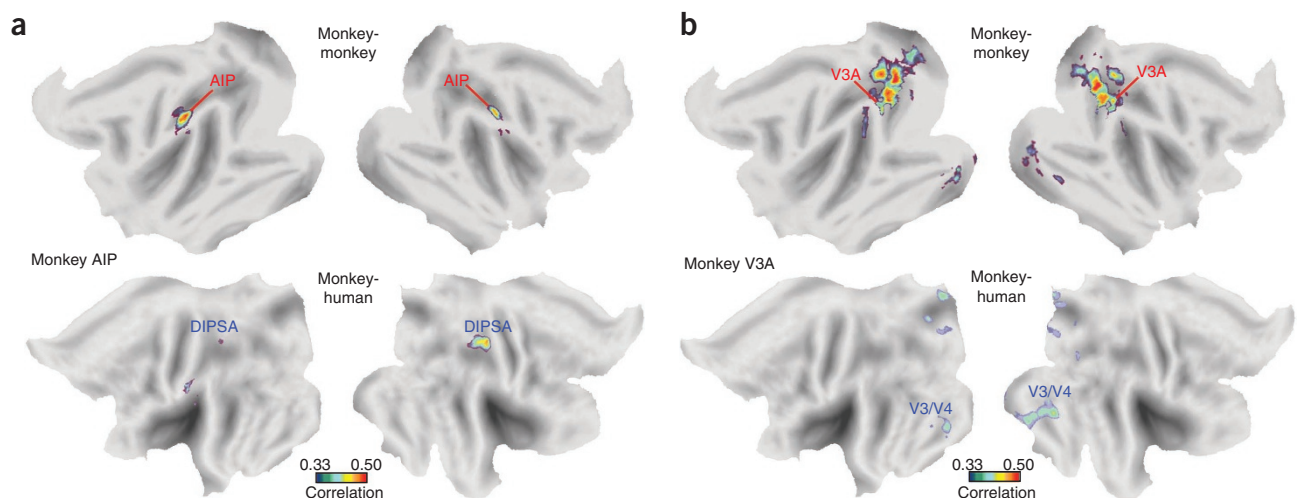
Figure 3 | Intra- and interspecies activity correlation from monkey areas PITd and CITd. (**a**,**b**) Intra- and interspecies activity correlation maps (FDR of $q < 0.001$) from both left and right monkey PITd (**a**) and CITd (**b**). The correlation maps are shown only for the same hemisphere in which the seed area is positioned. The borders of monkey areas MT, PITd and CITd are drawn over the monkey flat map. The same borders after monkey-to-human cortical surface expansion are drawn over the human flat map. aTOS, anterior transverse occipital sulcus and PCu, precuneus. Correlations are expressed in r values.

models[8,9]. To test for proposed functional reorganizations in ventral stream regions[17,18], we carried out an ISAC analysis on two neighboring inferotemporal areas (dorsal posterior and central inferotemporal areas, PITd and CITd) located rostral to area MT in the monkey[16]. Our analyses showed distinct intra- and interspecies correlation maps for the two regions (**Fig. 3**). The ISAC map for PITd revealed a network including posterior PITd (pPITd), the posterior middle temporal gyrus (pMTG), the posterior superior temporal sulcus (pSTS) and the precuneus (**Fig. 3a**). With the exception of the latter area, these data are consistent with a simple cortical surface expansion model[17]. In contrast, the ISAC map for neighboring monkey area CITd (**Fig. 3b**), located ventrorostrally with respect to MT and PITd areas, showed the human anterior transverse occipital sulcus (aTOS), located dorso-caudally to human MT+ (ref. 19). Therefore, activations of adjacent areas (PITd and CITd) in the monkey brain seem to be functionally related to response patterns in human

pSTS, pMTG, pPITd and aTOS that are, topographically speaking, sharply divergent. This pattern does not fit with the systematic topographical shift and expansion predicted by cortical surface expansion models. Instead, the results are more consistent with an evolution-driven functional reorganization of parts of the ventral stream.

Next, we tested the hypothesis that stronger functional reorganizations tend to occur in regions with greater anatomical expansion[7], by applying the ISAC analysis on the anterior intraparietal (AIP) area and area V3A of the monkey. These two higher-level areas are located in regions with higher and lower extent of cortical expansion, respectively (about 20-fold and threefold), as compared to the mean (tenfold) across the cortex[5]. When seeding in monkey AIP area[20], we found similar responses in the anterior dorsal intraparietal sulcus area (DIPSA), most likely its human homolog[6,21] (**Fig. 4a**). AIP area and DIPSA are both activated by the observation of hand movement[10,22], and belong to the monkey and human

Figure 4 | Intra- and interspecies activity correlation maps (FDR of $q < 0.001$) from monkey areas AIP and V3A. (**a**) Monkey and human areas showing activity correlated with that in monkey AIP. (**b**) Monkey and human areas showing activity correlated with that in monkey V3A. DIPSA: anterior dorsal intraparietal sulcus area. Correlations are expressed in r values.
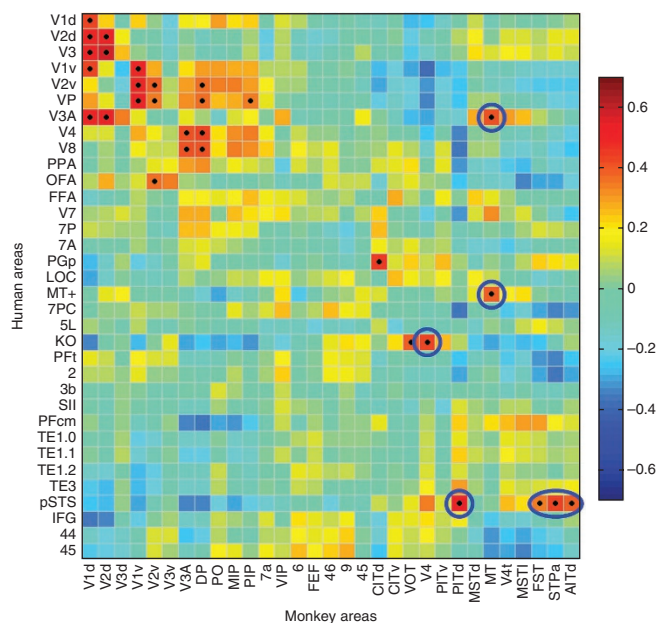
Figure 5 | Interspecies activity correlations between monkey and human areas. The ISAC matrix, calculated on 31 monkey and 34 human areas with consistent fMRI responses, is sorted so that areas with the strongest intraspecies correlations are neighboring. Functional correspondence, defined on the basis of the Pearson's correlation test (FDR of $q < 0.001$), are marked with a black dot. Interspecies correspondences that are commented in the text are marked with either circular or oval-shaped borders.

mirror neuron system, respectively. Conversely, seeding in monkey area V3A[3] revealed no substantial functional correspondence with human area V3A, whereas the largest interspecies correlation was unexpectedly located in the human ventral occipital areas including area V4 (**Fig. 4b**). Hence, the extent of anatomical cortical expansion did not necessarily predict the extent of functional reorganization in individual areas in these regions.

Large-scale analysis of interspecies correspondences

Our ISAC results indicate several putative functional similarities between areas of the monkey and the human cortex whose anatomical locations do not correspond (**Figs. 3b** and **4b**). To allow larger-scale inferences, we performed an ISAC analysis across all cortical regions that were activated by the stimuli (**Fig. 1d**). Accordingly, we defined 31 monkey and 34 human areas spanning the intersubject activity correlation map of the respective species (**Fig. 2**), and then compared the stimulus-related responses of these areas by temporal correlation. First, we analyzed the reliability of this analysis by assessing the similarity of the ISAC matrices obtained from each of the two halves of either the monkey or human data (**Supplementary Fig. 9**). Their structures largely corresponded (spatial correlation between matrices, calculated for monkeys 1–2 and 3–4, and for humans 1–12 and 13–24, was $r = 0.886$, $P < 0.001$ and $r = 0.864$, $P < 0.001$, respectively). Next we examined the strongest correlations (FDR of $q < 0.001$) in the ISAC matrix calculated using the complete datasets (**Fig. 5**). In general, the matrix showed results consistent with those found through the seed-based ISAC mapping. For instance, we confirmed monkey-human functional correspondences for the early visual areas, and between monkey MT and human MT+ areas (**Supplementary Figs. 7** and **8**). As shown

previously by ISAC mapping, we also observed comparable activity between areas that do not anatomically correspond (**Fig. 5**). As an example, monkey area MT showed similar responses not only to human area MT+ ($r = 0.41$, $P < 0.001$) but also to human V3A ($r = 0.37$, $P < 0.001$); conversely, responses in human area MT+ and monkey V3A were substantially unrelated ($r = -0.10$, $P = 0.858$). This result is consistent with studies suggesting functional differences between monkey and human V3A, particularly with regard to their motion sensitivities[3,6]. Close inspection of the ISAC matrix revealed additional interspecies similarities (FDR of $q < 0.001$), which provide a more complete picture of putative evolution-driven functional reorganizations (**Fig. 5**). For instance, fMRI signals of human pSTS correlated with those of monkey PITd ($r = 0.54$), but also with signals in monkey fundal superior temporal area ($r = 0.35$), anterior superior temporal polysensory area ($r = 0.43$) and dorsal anterior inferotemporal area ($r = 0.39$). We also found similar functional responses in human kinetic occipital region and monkey V4 region ($r = 0.42$), areas for which neuroimaging and electrophysiological studies suggest a sensitivity to kinetic motion boundaries[23,24]. This finding showed the potential of large-scale ISAC analyses to provide specific targets for new functional investigations between species. Reverse correlation analyses may be used to probe whether patterns of specific stimuli evoke consistent fMRI responses in selected brain areas[10].

DISCUSSION
The non-human primate visual system has become a model for the human visual system[4,25], on the presumption that similar functions and thus computations are carried out by anatomically corresponding cortical circuitries (the principle of homology or cortical proximity)[7]. Our findings suggest that functional reorganization is not strictly related to cortical expansion processes and may result from mechanisms whereby neuronal circuitries are adapted and recycled to enable more complex cognitive functions[8,9].

Our study with natural vision data has several limitations. First, the interpretation of our results depends on the assumption that individuals in the two species engage the same processes. During observation of the movie, the monkeys' understanding of spoken language, actions and plot cannot be compared to that of human subjects. Still large parts of the brain were engaged by the powerful multimodal sensory stimuli, as shown by our findings. Controlled stimuli are needed to compare functional similarities and differences in higher-order functions. Second, correlations across visual and other stimulus properties can occur during natural vision, potentially leading to false positive results. Again, this may be minimized using well-controlled stimuli and experimental designs. Third, the ISAC method relies on the definition of seed areas to reveal analogies across the cortex. To overcome this disadvantage, we are working on data-driven approaches to define functional correspondences independently of seed definitions.

We suggest that the ISAC approach will permit comprehensive studies of functional correspondences between higher-level areas in the primate brain, using methods devoid of spatial constraints on the cortical surface. When applied to fMRI data obtained from monkeys and humans performing specific sensory and cognitive tasks, the ISAC method may clarify whether specific functions are preserved in areas that anatomically correspond, are absent in one of the two species or are shifted to other cortical locations. This approach

will be critical for shedding light on evolution-driven changes in the functional architecture of the primate brain, and ultimately, for clarifying how human-specific cognitive abilities emerged.

METHODS
Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturemethods/.

Note: Supplementary information is available on the Nature Methods website.

AUTHOR CONTRIBUTIONS
W.V., M.C., G.L.R., D.M. and G.A.O. designed the research; D.M., V.B. and M.G.P. collected the data; D.M. analyzed the data under the supervision of U.H. and W.V.; D.M. and W.V. wrote the first draft of the manuscript, which all authors revised and approved.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

Published online at http://www.nature.com/naturemethods/.
Reprints and permissions information is available online at http://www.nature.com/reprints/index.html.

1. Tootell, R.B., Tsao, D. & Vanduffel, W. Neuroimaging weighs in: humans meet macaques in "primate" visual cortex. *J. Neurosci.* **23**, 3981–3989 (2003).
2. Nakahara, K., Hayashi, T., Konishi, S. & Miyashita, Y. Functional MRI of macaque monkeys performing a cognitive set-shifting task. *Science* **295**, 1532–1536 (2002).
3. Vanduffel, W. *et al.* Extracting 3D from motion: differences in human and monkey intraparietal cortex. *Science* **298**, 413–415 (2002).
4. Orban, G.A., Van Essen, D. & Vanduffel, W. Comparative mapping of higher visual areas in monkeys and humans. *Trends Cogn. Sci.* **8**, 315–324 (2004).
5. Van Essen, D.C. & Dierker, D.L. Surface-based and probabilistic atlases of primate cerebral cortex. *Neuron* **56**, 209–225 (2007).
6. Orban, G.A. *et al.* Mapping the parietal cortex of human and non-human primates. *Neuropsychologia* **44**, 2647–2667 (2006).
7. Striedter, G.F. Brain homology and function: an uneasy alliance. *Brain Res. Bull.* **57**, 239–242 (2002).
8. Anderson, M.L. Neural reuse: a fundamental organizational principle of the brain. *Behav. Brain Sci.* **33**, 245–266 (2010).
9. Dehaene, S. & Cohen, L. Cultural recycling of cortical maps. *Neuron* **56**, 384–398 (2007).
10. Hasson, U., Nir, Y., Levy, I., Fuhrmann, G. & Malach, R. Intersubject synchronization of cortical activity during natural vision. *Science* **303**, 1634–1640 (2004).
11. Vincent, J.L. *et al.* Intrinsic functional architecture in the anaesthetized monkey brain. *Nature* **447**, 83–86 (2007).
12. Hasson, U., Malach, R. & Heeger, D.J. Reliability of cortical activity during natural stimulation. *Trends Cogn. Sci.* **14**, 40–48 (2010).
13. Shepherd, S.V., Steckenfinger, S.A., Hasson, U. & Ghazanfar, A.A. Human-monkey gaze correlations reveal convergent and divergent patterns of movie viewing. *Curr. Biol.* **20**, 649–656 (2010).
14. Denys, K. *et al.* Visual activation in prefrontal cortex is stronger in monkeys than in humans. *J. Cogn. Neurosci.* **16**, 1505–1516 (2004).
15. Allman, J.M. & Kaas, J.H. Representation of the visual field in striate and adjoining cortex of the owl monkey (*Aotus trivirgatus*). *Brain Res.* **35**, 89–106 (1971).
16. Felleman, D.J. & Van Essen, D.C. Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cortex* **1**, 1–47 (1991).
17. Jastorff, J. & Orban, G.A. Human functional magnetic resonance imaging reveals separation and integration of shape and motion cues in biological motion processing. *J. Neurosci.* **29**, 7315–7329 (2009).
18. Tsao, D.Y., Moeller, S. & Freiwald, W.A. Comparing face patch systems in macaques and humans. *Proc. Natl. Acad. Sci. USA* **105**, 19514–19519 (2008).
19. Hasson, U., Harel, M., Levy, I. & Malach, R. Large-scale mirror-symmetry organization of human occipito-temporal object areas. *Neuron* **37**, 1027–1041 (2003).
20. Durand, J.B. *et al.* Anterior regions of monkey parietal cortex process visual 3D shape. *Neuron* **55**, 493–505 (2007).
21. Culham, J.C. & Kanwisher, N.G. Neuroimaging of cognitive functions in human parietal cortex. *Curr. Opin. Neurobiol.* **11**, 157–163 (2001).
22. Peeters, R. *et al.* The representation of tool use in humans and monkeys: common and uniquely human features. *J. Neurosci.* **29**, 11523–11539 (2009).
23. Mysore, S.G., Vogels, R., Raiguel, S.E. & Orban, G.A. Processing of kinetic boundaries in macaque V4. *J. Neurophysiol.* **95**, 1864–1880 (2006).
24. Van Oostende, S., Sunaert, S., Van Hecke, P., Marchal, G. & Orban, G.A. The kinetic occipital (KO) region in man: an fMRI study. *Cereb. Cortex* **7**, 690–701 (1997).
25. Sereno, M.I. & Tootell, R.B. From monkeys to humans: what do we now know about brain homologies? *Curr. Opin. Neurobiol.* **15**, 135–144 (2005).

ONLINE METHODS

Subjects. Four rhesus monkeys (*M. mulatta*, three males and one female, 4–6 kg, 4–7 years old) and 24 right-handed young, healthy, Italian-speaking volunteers (9 males and 15 females, 20–31 years old) participated in the study. Animal care procedures met the Belgian and European guidelines, and were approved by the K.U. Leuven Medical School. Human volunteers were informed about the experimental procedures and signed a written informed consent. The study design was approved by the local Ethics Committees of both the K.U. Leuven and the Chieti University, for experiments with monkeys and humans, respectively.

For the health and welfare of the animals, we followed the Belgian and EU regulations (EU directive on the protection of animals used for scientific purposes 2010/63/EU). The macaques were pair- or group-housed in the primate facility of the K.U. Leuven Medical School. The cages provide adequate space for housing multiple macaques (2–5) and each animal room has a large playing pen equipped with toys and enrichment tools. Animals' access to water was restricted between experiments. The monkeys were trained using operant conditioning techniques and they could drink until satiated during the experiments.

Data collection: behavioral task. We carried out a natural-vision experiment, in which the subjects watched and listened to 30 min of the Italian version of the movie *The Good the Bad and the Ugly*[10], from 16 min 48 s to 46 min 48 s. The movie was divided into three clips of 10 min each. The movie clips were presented six times to the monkeys, and once to the human subjects.

Experimental setup. Human volunteers lay in a supine position and watched the clips through a mirror tilted 45 degrees toward a translucent screen onto which the movie was projected at a frame rate of 60 Hz. The subjects were allowed to watch the movie clips freely while keeping their gaze within the projection area (24 × 10.2 visual degrees, 640 × 272 pixels). A similar free-viewing condition was achieved in monkeys by rewarding them with juice when their gaze was kept within the 24 × 10.2 degree virtual window covering the projected movie[3]. Monkeys were prepared for scanning as in our previous studies[3,26]. Specifically, a bolus of microcrystalline-iron-oxide nanoparticles (MION; Sinerem, Guerbet; 6–10 mg kg^{-1}) was injected into the femoral vein of the animal before fMRI scanning. For both monkeys and humans, eye position was monitored using pupil-corneal reflection tracking at 120 Hz (Iscan). Furthermore, magnetic resonance–compatible headphones with ear-cup pads were used to deliver the acoustic stimuli associated with the movie and to shield the ears from environmental noise.

fMRI data acquisition. Monkey fMRI was performed with a 3T MR Siemens Trio scanner in Leuven, Belgium. The functional images were collected using a gradient-echo T2-weighted echo-planar sequence (40 slices, 84 × 84 in-plane matrix, repetition time (TR) = 2,000 ms, echo time (TE) = 19 ms, flip angle = 75°, voxel size = 1.25 mm × 1.25 mm × 1.25 mm). In addition, high-resolution, T1-weighted anatomical images (magnetization-prepared rapid gradient echo (MP-RAGE) sequence, TR = 2,200 ms, TE = 4.06 ms, voxel size = 0.5 mm × 0.5 mm × 0.5 mm) were collected in separate sessions under ketamine-xylazine anesthesia to provide the anatomical reference for the functional scans.

fMRI in humans was performed with a 3T MR Philips Achieva scanner in Chieti, Italy. The functional images were obtained using T2-weighted echo-planar images (EPIs) with blood oxygen level–dependent contrast using SENSE imaging. EPIs comprised 32 axial slices acquired continuously in ascending order and covering the entire brain (32 slices, 230 × 230 in-plane matrix, TR = 2,000 ms, TE = 35 ms, flip angle = 90°, voxel size = 2.875 mm × 2.875 mm × 3.5 mm). A three-dimensional high-resolution T1-weighted image was collected by means of an MP-RAGE sequence TR = 8.1 ms, TE = 3.7 ms, voxel size = 0.938 mm × 0.938 mm × 1 mm).

Eye-gaze analysis. We analyzed eye-movement trajectories during fMRI scanning. Eye traces were converted to visual degrees by a four-point spatial projection calibration. Next, the variability in eye positions along the *x* and *y* axes was quantified by standard deviation. To statistically assess differences between humans and monkeys with regard to eye-position variability, an unpaired *t*-test was calculated. Furthermore, we measured eye movements by computing speeds in the *x* and *y* directions in the eye traces and calculating the square root of the sum of their squares. We then measured temporal correlations between eye movements across subjects[13]. This was done for each monkey, within monkey and human groups, and finally between the two groups. An unpaired *t*-test between monkey and human intersubject correlations was calculated as well.

fMRI preprocessing. fMRI data preprocessing was performed with the SPM5.0 software package[27] (Wellcome Trust Centre for Neuroimaging). We preprocessed functional time series to compensate for slice-dependent time shifts, head motion and linear trends. We spatially warped the monkey and human data to F99 and MNI atlas spaces, respectively. The final spatial resolution was 1 mm and 3 mm isotropic, respectively, for the two species. To reduce the contributions of artifactual sources, we removed signals from a ventricular region of interest and a region centered in the white matter[11] using a regression technique. Next, we spatially smoothed the data with a Gaussian kernel at 1.5 and 4.5 mm FWHM, for monkeys and humans, respectively.

We applied temporal preprocessing to the fMRI data to minimize signal differences arising from the different hemodynamic response functions (HRFs). The deconvolution of the fMRI time series[28] is typically used to correct for different HRFs, particularly when the timing of the experimental events is available. As we intended that the ISAC method should not rely on this information, we used an alternate approach. We convolved the monkey and human fMRI time courses with a canonical human and monkey HRF[26,29,30], respectively (**Supplementary Fig. 1**). In this manner, we could make allowance for different hemodynamic peak delays and spectral contents (**Supplementary Fig. 2** and **Supplementary Note**). To avoid any border effects owing to signal convolution, we removed the first 20 and the last ten functional volumes from each run. Finally, we converted the time courses related to the three consecutive movie blocks to *z* scores and then concatenated them. As a result, each dataset representing a single movie repetition was composed of 810 functional volumes. For each selection of datasets, an average dataset was constructed by averaging the time courses in corresponding voxels. This procedure allowed us to maximize the relative contribution of stimulus-evoked responses exceeding spontaneous activity in our analysis.

Conversion from volumes to surfaces. The conversion from volumes to surfaces was performed with Caret 5.61 software[5]. The surface maps were visualized on a flattened cortex, together with the borders of anatomically and/or functionally defined areas. Anatomical areas in the monkey were defined based on the cortical parcellation of ref. 16, included in Caret software, whereas functional areas were designated based on results from our previous studies[3,4,6,20]. Human anatomical areas were defined on the basis of the cytoarchitectonical maps available in the SPM Anatomy Toolbox, whereas human functional areas were defined from our localizers[10,17] and the visuotopic maps included in Caret software[5].

Analysis of fMRI response reliability within a species. To estimate the relative contribution of stimulus-driven activity to the fMRI data, we calculated voxel-by-voxel temporal correlations across subjects or intersubject correlation within a species[10]. This analysis was performed independently for each individual monkey, and for monkeys and humans at the group level. Following Bartlett's theory to account for autocorrelation in an fMRI signal[11], the degrees of freedom were defined as the total number of time used to calculate the correlation (810 in our datasets) divided by a correction factor c, defined as the time integral of the square of the lagged autocorrelation function. The latter was computed by fast fourier transform (FFT)[11] for an estimation across all monkey and human brain voxels. The distribution of correction factors across gray matter voxels was computed for the average monkey (deformed to the human space to equalize the number of voxels) and human datasets (**Supplementary Fig. 3**).

We estimated an autocorrelation-based correction factor of 6.76, that is, the mean of the joint distribution of monkey and human values. Based on the degrees of freedom defined as $810 / 6.76 - 2 = 117.82$, we converted the correlations to probability values, and applied the FDR method to account for multiple comparisons. Accordingly, we thresholded the monkey and human intersubject correlation maps at FDR of $q < 0.05$. Finally, we defined a monkey and a human common signal as the average of the fMRI signals showing intersubject correlation.

Interspecies activity correlation. We used regression analysis[11] to attenuate any common signals in the fMRI data (as defined in the intraspecies reliability analysis), thus removing any effect these might have on similarities detected between pairs of time courses. To detect similar functional processing based on similar fMRI responses, we used temporal correlation to compare time courses extracted from the respective areas of the two species. We calculated intraspecies and interspecies activity correlation maps, by correlating the seed time course with all the voxel time courses in the brains of the same (**Fig. 1a**) and the other species (**Fig. 1b,c**). To identify brain areas with responses similar to that in the seed, we thresholded the maps at FDR of $q < 0.001$. In addition, we performed pairwise comparisons between selected monkey and human areas, so that we formed an ISAC matrix (**Fig. 1d**). Again, we thresholded the ISAC matrix at FDR of $q < 0.001$ to detect interspecies similarities.

Analysis of ISAC reliability. To assess the reproducibility of the ISAC results, we first focused on early visual areas in monkeys and humans. As the monkeys viewed the movie multiple times, we calculated the ISAC values between the whole human dataset and subsets of the monkey data corresponding to single movie repetitions. To test for the presence of differences in these correlations across movie repetitions, we performed a one-way Kruskal-Wallis analysis of variance on them.

In addition, we conducted a reliability analysis on the ISAC mapping. We selected monkey area MT and human area MT+ as seeds, and then mapped the intra and interspecies correlations on the whole monkey and human datasets using the seed time courses derived from monkeys 1–2 and 3–4, and humans 1–12 and 13–24, respectively. We assessed the correspondence of ISAC maps from either monkey or human seeds by spatial correlation.

Finally, we tested the reliability of the ISAC matrix by comparing the results obtained from monkeys 1–2 and 3–4, and from humans 1–12 and 13–24. To assess the correspondence between the resulting ISAC matrices, we again used spatial correlations.

26. Vanduffel, W. *et al.* Visual motion processing investigated using contrast agent-enhanced fMRI in awake behaving monkeys. *Neuron* **32**, 565–577 (2001).
27. Friston, K.J. *et al. Statistical Parametric Mapping: The Analysis of Functional Brain Images*, 1st edn. (Academic Press, Oxford, 2007).
28. Penny, W., Ghahramani, Z. & Friston, K. Bilinear dynamical systems. *Phil. Trans. R. Soc. Lond. B* **360**, 983–993 (2005).
29. Leite, F.P. *et al.* Repeated fMRI using iron oxide contrast agent in awake, behaving macaques at 3 Tesla. *Neuroimage* **16**, 283–294 (2002).
30. Heeger, D.J. & Ress, D. What does fMRI tell us about neuronal activity? *Nat. Rev. Neurosci.* **3**, 142–151 (2002).