to regions such as dorsal raphe, ventral tegmental area, hypothalamus, and amygdala, mPFC exerts top-down controls on serotonin and dopamine release, endocrine function, and fear response. All of these could contribute to key features of the dominance behaviors, including aggressiveness, stress responsiveness, and fearfulness. It will be of interest to determine which of these mPFC downstream circuits are specifically involved in setting the dominance hierarchy and to investigate how the dominance rank is initiated and maintained by differential neuronal activities in these circuits. Likewise, it will also be important to understand how the behavioral specificity of mPFC is generated by distinct upstream inputs, given the multiple functions that mPFC has been implicated in [reviewed by (*30*) and, recently, (*31*–*34*)]. The identification of a neural substrate of dominance hierarchy should provide new insights into the coding of a fundamental social behavior in the mammalian nervous system.

References and Notes

1. E. O. Wilson, *Sociobiology: The New Synthesis* (Harvard Univ. Press, Cambridge, MA, 1975).
2. I. S. Bernstein, *Behav. Brain Sci.* **4**, 419 (1981).
3. R. M. Sapolsky, *Science* **308**, 648 (2005).
4. S. R. Yeh, R. A. Fricke, D. H. Edwards, *Science* **271**, 366 (1996).
5. C. Drews, *Behaviour* **125**, 283 (1993).
6. D. G. Frankel, T. Arbel, *Int. J. Behav. Dev.* **3**, 287 (1980).
7. J. Masur, M. A. Benedito, *Nature* **249**, 284 (1974).
8. D. A. Dewsbury, *Anim. Behav.* **39**, 284 (1990).
9. A. Mehrabian, *Curr. Psychol.* **14**, 261 (1996).
10. D. D. Cummins, *Synthese* **122**, 3 (2000).
11. G. Lindzey, H. Winston, M. Manosevitz, *Nature* **191**, 474 (1961).
12. A. S. Garfield *et al.*, *Nature* **469**, 534 (2011).
13. H. Arakawa, D. C. Blanchard, R. J. Blanchard, *Behav. Brain Res.* **176**, 27 (2007).
14. S. Y. Long, *Anim. Behav.* **20**, 10 (1972).
15. L. C. Drickamer, *Behav. Processes* **53**, 113 (2001).
16. J. Nyby, G. A. Dizinno, G. Whitney, *Behav. Biol.* **18**, 285 (1976).
17. D. Benton, J. C. Dalrymplealford, P. F. Brain, *Anim. Behav.* **28**, 1274 (1980).
18. C. F. Zink *et al.*, *Neuron* **58**, 273 (2008).
19. J. Y. Chiao, *Curr. Opin. Neurobiol.* **20**, 803 (2010).
20. H. B. Uylings, H. J. Groenewegen, B. Kolb, *Behav. Brain Res.* **146**, 3 (2003).
21. R. R. Holson, *Physiol. Behav.* **37**, 239 (1986).
22. H. Marie, W. Morishita, X. Yu, N. Calakos, R. C. Malenka, *Neuron* **45**, 741 (2005).
23. S. G. McCormack, R. L. Stornetta, J. J. Zhu, *Neuron* **50**, 75 (2006).
24. H. L. Hu *et al.*, *J. Neurosci.* **28**, 7847 (2008).
25. J. J. Zhu, Y. Qin, M. Zhao, L. Van Aelst, R. Malinow, *Cell* **110**, 443 (2002).
26. S. A. Kushner *et al.*, *J. Neurosci.* **25**, 9721 (2005).
27. J. J. Zhu, J. A. Esteban, Y. Hayashi, R. Malinow, *Nat. Neurosci.* **3**, 1098 (2000).
28. J. J. Zhu, *J. Neurosci.* **29**, 6320 (2009).
29. D. M. Amodio, C. D. Frith, *Nat. Rev. Neurosci.* **7**, 268 (2006).
30. R. P. Vertes, *Synapse* **51**, 32 (2004).
31. H. E. Covington 3rd *et al.*, *J. Neurosci.* **30**, 16082 (2010).
32. O. Yizhar *et al.*, *Nature* **477**, 171 (2011).
33. K. Guillem *et al.*, *Science* **333**, 888 (2011).
34. D. Tse *et al.*, *Science* **333**, 891 (2011).

Acknowledgments: We thank J. Zhu for the gifts of pSindbis GluR4 and R4Ct constructs and discussion on GluR4; R. Malinow for support of the initial exploration of the tube test in his laboratory; M. Poo, H. Kessels, J. Feldman, and R. Sapolsky for discussion and critical reading of the manuscript; J. Yan for help with statistics; B. Lu for the idea of agonistic behavior test; B. Zhang, K. Zhang, and M. Streets for technical help; Y. Yanagawa for the Gad67-GFP mouse; and X. Yu for ultrasound equipment. The work was supported by Chinese 973 Program (2011CBA00400), Projects of the Scientific Research Foundation, the Hundreds of Talents Program, and the Shanghai Pujiang Talent Program to H.H. Author contributions: F.W. performed most experiments. J.Z. participated in the behavioral and viral injection experiments. F.W., J.Z., and H.H. analyzed data and prepared the figures. H.Z, Q.Z., and Z.L. assisted in experiments. H.H. designed the study and wrote the manuscript.

Supporting Online Material

www.sciencemag.org/cgi/content/full/science.1209951/DC1
Materials and Methods
SOM Text
Figs. S1 to S10
References

17 June 2011; accepted 9 September 2011
Published online 29 September 2011;
10.1126/science.1209951

Social Network Size Affects Neural Circuits in Macaques

J. Sallet,[1,2]*† R. B. Mars,[1,2]* M. P. Noonan,[1,2]* J. L. Andersson,[2] J. X. O'Reilly,[2] S. Jbabdi,[2] P. L. Croxson,[1,3] M. Jenkinson,[2] K. L. Miller,[2] M. F. S. Rushworth[1,2]

It has been suggested that variation in brain structure correlates with the sizes of individuals' social networks. Whether variation in social network size causes variation in brain structure, however, is unknown. To address this question, we neuroimaged 23 monkeys that had been living in social groups set to different sizes. Subject comparison revealed that living in larger groups caused increases in gray matter in mid-superior temporal sulcus and rostral prefrontal cortex and increased coupling of activity in frontal and temporal cortex. Social network size, therefore, contributes to changes both in brain structure and function. The changes have potential implications for an animal's success in a social context; gray matter differences in similar areas were also correlated with each animal's dominance within its social network.

The evolution of primate brains is thought to be associated with the demands of living in a complex social environment (*1*). Recent evidence shows that differences in brain structure correlate with variation in individuals' social network size (*2*); some brain structures are larger in people in regular contact with a larger number of relatives, friends, and colleagues. However, the direction of cause and effect underlying this phenomenon is unknown. Although this issue has not been directly investigated, sensorimotor experience is known to lead to brain structural changes even during adulthood (*3*, *4*). For instance, learning to use a tool increases gray matter density in the intraparietal sulcus (IPS), caudal superior temporal sulcus (STS), and somatosensory cortex in the rhesus macaque (*Macaca mulatta*) (*3*). Here, we exploit the pseudo-randomized assignment of individual animals to social groups in a research colony (*5*) to demonstrate that variation in young adult rhesus macaques' social environments changes structure and function in a distributed neural circuit centered on mid-STS, anterior cingulate cortex (ACC), and rostral prefrontal cortex (rPFC).

First, we conducted a deformation-based morphometric (DBM) analysis (*6*) of magnetic resonance imaging (MRI) scans of brain structure from 23 young adult [4.33 ± 0.52 years (mean ± SD)] monkeys (14 males) (*5*). Scanned animals were drawn from 34 animals from different groups within a research colony. The animals were housed in groups of between one and seven individuals. We considered the number of housemates of each monkey as a measure of social network size.

The organization of monkeys into groups was not randomized in a conventional sense but instead depended on factors that were independent of social characteristics; these included the requirements of independent programs of neuroscientific research and veterinary considerations [full details of housing arrangements are provided (*5*)]. A true randomization of animals would have been virtually impossible given numerous considerations, including the constraints imposed by the licensing of experimental procedures, the cost of such a project, and the potential for disruption to other research programs. While some unobserved variables might have contributed to the outcomes we report, group assignment was not carried out on the basis of social character-

[1]Department of Experimental Psychology, University of Oxford, Oxford OX1 3UD, UK. [2]Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), University of Oxford, Oxford OX1 3UD, UK. [3]Icahn Medical Institute, Mount Sinai School of Medicine, New York, NY 10029, USA.

*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: jerome.sallet@psy.ox.ac.uk

istics, and it was not the case that less sociable animals were housed together in smaller groups. Although one might imagine that a very unsociable animal might be identified and isolated, this does not imply that the next most unsociable animals would be housed together in a duo and the next most in a trio and so on. The one singly housed animal in the current experiment was an individual that was left after other members of the group had been used in other procedures. [Results after data from the singleton and even duos are omitted are also shown (*5*).] In summary, the assignment of group size in the current experiment is as close to randomized assignment as is currently feasible. Because the social network size is a parameter that is not controlled by the animals, then, in this context, any inter-individual brain differences that are correlated with social network size will be a consequence of the imposed social network size.

The constitutions of the groups studied were defined 0.53 ± 0.81 year after the animals' arrival in the facilities. In all cases, animals had been in a group of the stated size for some time (1.22 ± 0.6 years) before scanning. In addition to social network size, the age, weight, sex, and the number of MRI structural scans contributing to each individual's average structural MRI scan were included as regressors in a nonparametric general linear model (GLM) analysis. The dependent variable analyzed was the determinant of the Jacobian matrix from the nonlinear registration for each individual's structural scan, a scalar value that represents the amount each voxel in an individual's brain would need to be expanded or compressed to match the group-average brain. This method has proven suitable for studying brain plasticity (*6*). We identified gray matter areas in which the Jacobian determinant was significantly related to a regressor ($P < 0.005$, volume > 5 mm^3).

Positive linear correlations were found between social network size and Jacobian determinants in several regions, most notably temporal cortex in mid-STS, adjacent inferior temporal (IT) gyrus, rostral superior temporal gyrus (STG), and temporal pole (Fig. 1, A and B, and table S3). No negative correlation was found. In the areas in which effects were found, and over the social network sizes we investigated here, average gray matter density increased by 5.42% ± 2.73 per

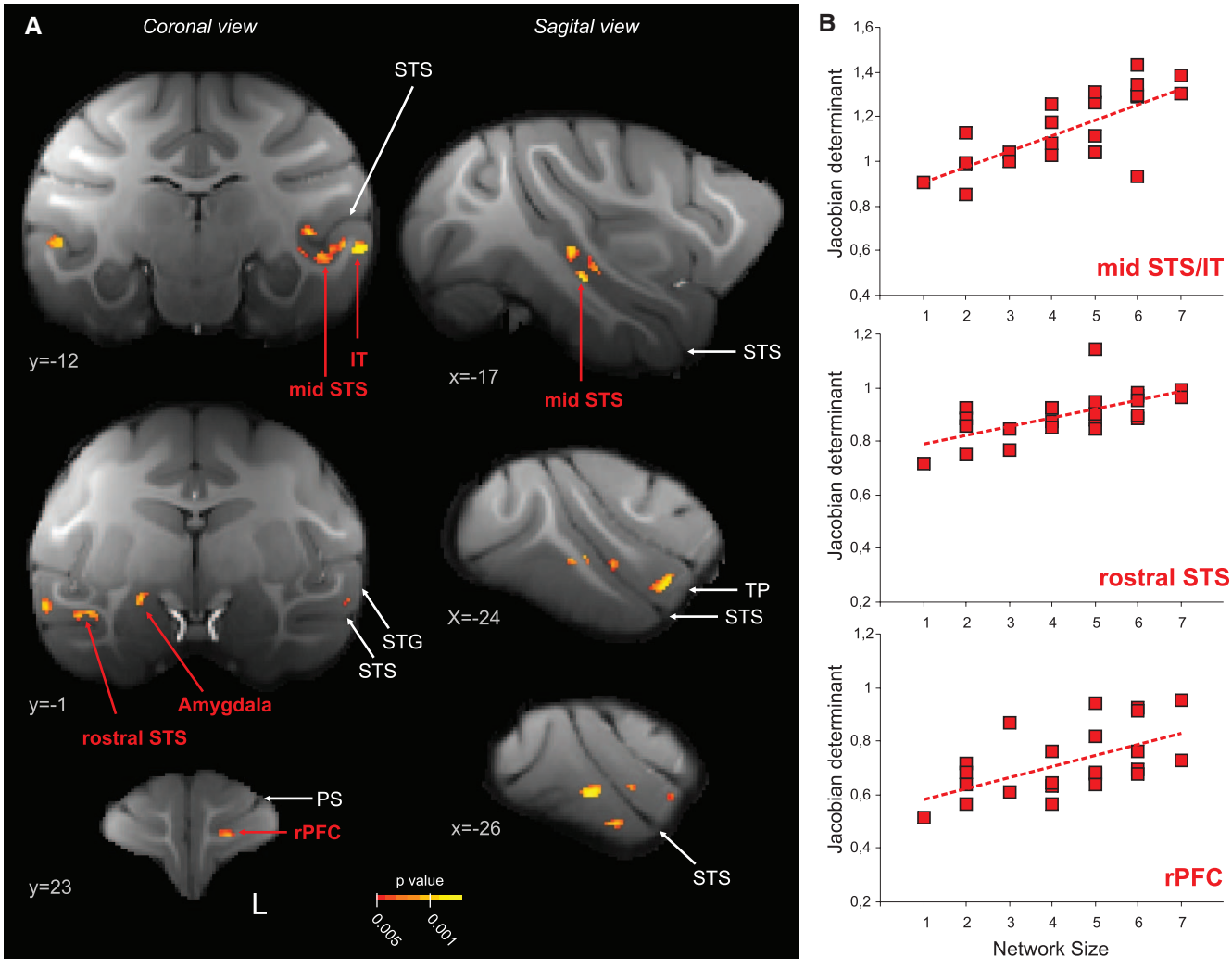

Fig. 1. Gray matter positively correlated ($P < 0.005$, cluster size > 5 mm^3) with network size in the temporal lobe and rPFC ($n = 23$). (**A**) Illustrations of the relationship between the determinant of the Jacobian matrix of the MRI warp fields applied during registration and network size at the centers of these regions. The *x* and *y* values correspond to coordinates (expressed in millimeters) within the Montreal Neurological Institute macaque rhesus template space. Red arrows indicate regions where network size effects were observed. White arrows indicate anatomical landmarks. PS, principal sulcus; STS, superior temporal sulcus; STG, superior temporal gyrus; IT, inferotemporal cortex; rPFC, rostral prefrontal cortex; TP temporal pole; L, left. (**B**) Illustration of relationship between network size and Jacobian determinants in the mid-STS/IT, rostral STS, and rPFC. Jacobian determinants greater than 1 indicate that voxels in an individual's MRI scan must be compressed to match the group template in MNI space.

member of the social network. The STS clusters were in regions that are, in monkeys, responsive to visually presented faces and body movements (*7*–*9*). Some of these areas have been shown to respond to such stimuli with an activity profile that resembles that of areas in the human caudal STS at the temporo-parietal junction (TPJ) (*8*). The rostral STG has been implicated in the encoding of vocalization in macaques and in the holding of semantic knowledge in humans (*10*, *11*). In macaques, lesions of the temporal pole disrupt emotional responsiveness (*12*). The gray matter increases in these areas could, therefore, reflect an increasing need to decode the significance of the facial expressions, gestures, and vocalizations of a greater number of individuals and combinations of individuals as network size increased.

A correlation was also found between social network and Jacobian determinants in the amygdala (Fig. 1A). Lesions of the amygdala also disrupt emotional responsiveness in both humans and macaques (*13*, *14*). Bickart and colleagues (*2*) have reported a similar correlation in human subjects but, unlike here, they were unable to determine whether differences in amygdala size were the consequence of differences in experienced social network size.

Our initial analysis also identified clusters in rPFC, in the rostral principal sulcus, at the border between dorsolateral prefrontal cortex (area 46) and the frontal pole (area 10) (Fig. 1, A and B, and table S3). In human subjects, an rPFC area rostral to the paracingulate sulcus, together with the STS, is active when predictions are made and updated about the intentions of others (*15*, *16*). Such predictions will have to be made about more individuals, and combinations of individuals, as social network size increases. It is possible that the rPFC region that we have identified in the macaques in the present study is similar to the human rPFC area (*17*, *18*). In humans, rPFC, together with STS and TPJ, is associated with "theory of mind" and prediction of another individual's overt behavior as well as their intentions (*15*, *16*). It is not clear if macaques have a theory of mind and are able to represent others' intentions (*15*, *16*), but they can make decisions based on inferences about what others can see (*19*), which might be a precursor of such an ability. There is also evidence that the activity of dorsolateral prefrontal neurons is modulated when choices are made in the context of an interactive game (*20*) and by the relative dominance of different individuals during interactions (*21*).

We searched for an effect of network size on other areas sometimes called "social brain" areas without success (*14*, *16*, *22*–*24*). For example, we did not observe significant correlation between network size and Jacobian determinants in the ventral premotor cortex, inferior parietal lobule, or anterior, lateral, and ventral IPS. These areas of the social brain have been described, in both humans and macaques, as part of the mirror neuron system (*16*). Neurons in these areas are responsive when macaques make movements and when they perceive the movements of others. It has been suggested that they are part of a system for understanding others' actions and intentions. Inclusion in a larger social network did not entail that other, nonsocial aspects of the environment were enriched, but it did entail that each individual spent more time engaged in social interactions with other individuals (Pearson's r = 0.9735, n = 11, P < 0.0001; fig. S1). It therefore seems, regardless of whatever role it may have in action perception, that the mirror neuron system

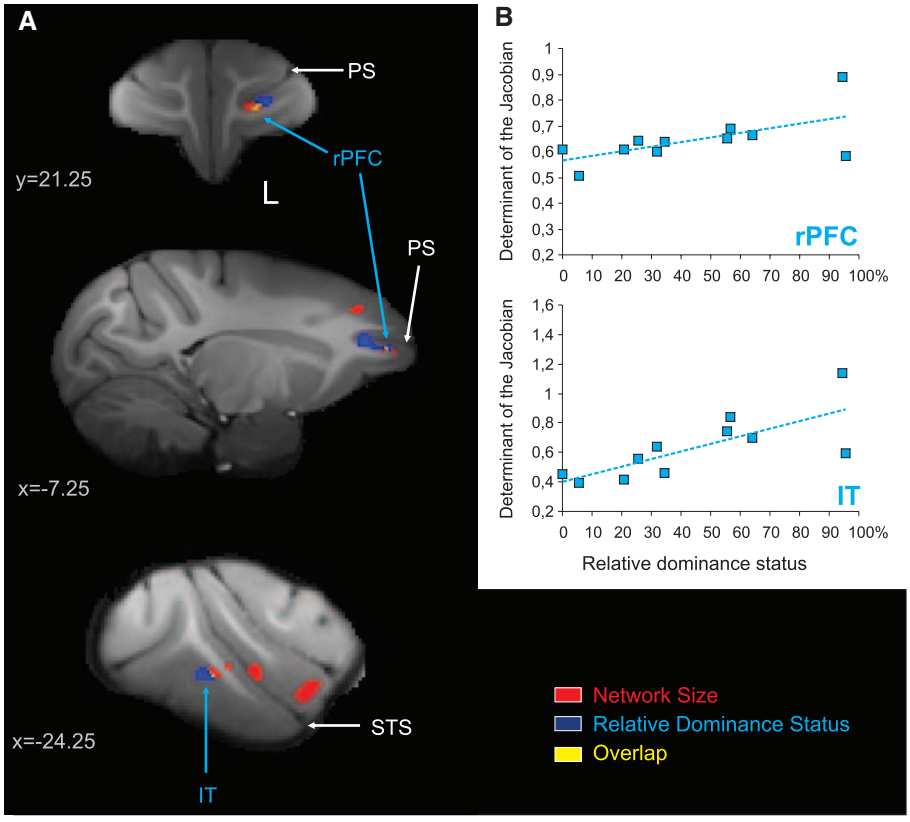

Fig. 2. Gray matter in rPFC correlated positively (P < 0.005, cluster size > 5 mm^3) with dominance (blue, n = 11), network size (red, n = 23), and conjunction of dominance and network size (yellow). (**A**) Illustrations of the relationship between the Jacobian determinant and relative dominance status at the centers of the overlapping regions. Blue arrows indicate regions where dominance status effects were observed. White arrows indicate anatomical landmarks. The x and y values correspond to coordinates (expressed in mm) within the MNI macaque rhesus template space. Abbreviations as for Fig. 1. (**B**) Illustration of relationship between relative dominance status and the Jacobian determinants in the rPFC and IT.

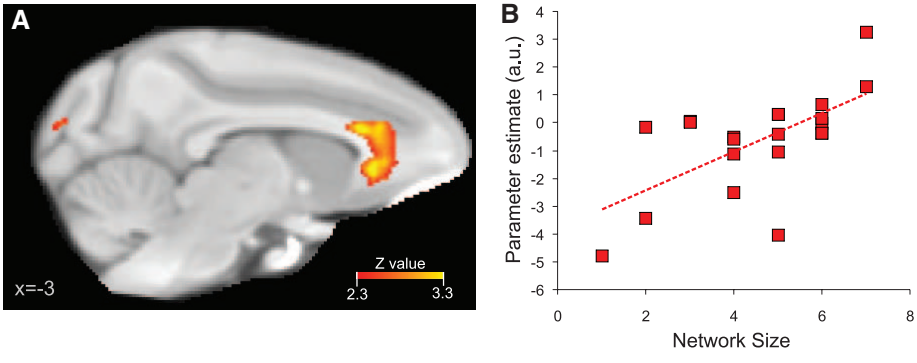

Fig. 3. (**A**) ACC gyrus regions in which BOLD signal indices of brain activity in the resting state were correlated with STS activity. (**B**) Illustration of correlation.

may not be challenged by the need to make more frequent inferences about a greater number of other individuals when social group sizes are larger.

It might be expected that increases in gray matter in a network of brain areas concerned with social cognition would lead to more successful social behavior. To test this proposition, we examined whether variation in the same brain structures was correlated with social rank after controlling for social network size. Social rank is an index of success in social settings and in macaques it is correlated with access to valued resources (*25*); social rank in male macaques is dependent on the ability to form coalitions, which in turn is dependent on the ability to form pair bonds (*25*). It is therefore plausible that social rank might be dependent on brain networks for social cognition.

We measured the social rank of 11 male macaques relative to other members of their social groups, in four groups, on the basis of observations of agonistic relationships (table S2). Each individual was assigned a cardinal index of social dominance (*26*). Not only did we ensure that individuals investigated in this more detailed analysis of behavior were all of the same sex, but we also controlled for the effect of social network size by selecting individuals from four groups of similar social network sizes (9 of 11 animals were taken from groups with either four or five members). This GLM analysis included the cardinal index of social dominance and additional regressors of age, weight, and social network size (despite the little variation in this factor for the individuals included in this analysis), and number of structural MRI scans contributing to each individual's average MRI scan. Gray matter in rPFC, in a region adjacent to the area where an rPFC effect of social network size was observed, increased with increasing social dominance (Fig. 2 and table S3). Average gray matter density increased by 0.31% ± 0.14 each time the relative dominance status was increased by 1%. In an additional test, we sought voxels in which there was an overlap of both social network and dominance effects. Smaller regions of IT and rPFC showed a conjunction effect (Fig. 2). That is, even after taking into account age, weight, and social network size, increased IT and rPFC size correlated with higher social rank. In summary, larger social networks cause changes in cortex in or adjacent to regions where gray matter is correlated with social dominance.

Finally, we investigated whether social network size affects brain activity as well as brain structure. We tested whether the coupling of activity, assessed using resting state functional MRI available from 21 of the same animals, increased with social network size. For each monkey a 1.5 mm by 1.5 mm by 1.5 mm region of interest "seed" area was positioned within the STS cluster, and the time series of the blood oxygen level–dependent (BOLD) signal was extracted. We then identified areas of functional connectivity with STS by regressing the STS functional time series against activity in every voxel in the brain, using a GLM in which age, weight, sex, and whole-brain mean time series were also included as co-regressors of no interest (*5*). First, we conducted region-of-interest analyses testing whether social network size increased functional coupling between the mid-STS seed and the rPFC regions identified in the previous structural analyses. The functional coupling between mid-STS activity and activity within a 2.5 mm by 2.5 mm by 1.5 mm region of interest covering the rPFC increased with increasing social network size (Pearson's $r = 0.386$, $n = 21$, $P = 0.042$). Similarly, the functional coupling between the temporal and frontal areas, IT and rPFC, that were identified in the DBM analysis of dominance increased with increasing dominance (Pearson's $r = 0.526$, $n = 11$, $P = 0.049$). The areas are monosynaptically interconnected (*27*).

More pronounced, however, were the results from the whole-brain analysis of functional coupling with STS, which identified increased coupling between activity in mid-STS and the ACC gyrus ($z > 2.3$, $P < 0.05$; Fig. 3, A and B, and table S5). An identical part of the macaque ACC gyrus has been implicated in the valuation of social information from conspecifics (*28*), and a related area has a similar function in humans (*22*). In both humans and macaques, it is specifically the ACC gyrus, rather than the adjacent ACC sulcus, that plays this role in social cognition. The ACC gyrus and mid-STS are also monosynaptically interconnected (*29*). Functional coupling between the STS and several extrastriate visual areas was also found (Fig. 3A and table S5). Several of the regions are part of the ventral visual processing stream that provides mid-STS with visual input.

In summary, we have identified a distributed neural circuit in which changes in structure and functional coupling occur as a function of social network size. The findings inform accounts of brain evolution that emphasize the pressure exerted by complexity of the social environment (*1*). One prediction of such accounts is that individual variation in brain anatomy should have implications for an individual's success within the social group, and we have demonstrated that brain structure correlates with measures of social dominance that remained constant over at least 4 months when group constitution did not change. The pattern of results is especially concordant with suggestions that complexity of social environments may have had a greater impact on specific brain circuits rather than the brain as a whole (*22*, *30*). These results may also have implications for understanding changes seen in neural circuits for social cognition in clinical conditions associated with alterations in social interaction; changes in brain areas may be partly a consequence, and not just the cause, of alterations in social interactions. Finally, the results raise the possibility that individual differences in patterns of inter-regional coupling of human brain activity measured in the resting state are a function of variation in social network size.

References and Notes

1. R. I. Dunbar, S. Shultz, *Science* **317**, 1344 (2007).
2. K. C. Bickart, C. I. Wright, R. J. Dautoff, B. C. Dickerson, L. F. Barrett, *Nat. Neurosci.* **14**, 163 (2011).
3. M. M. Quallo *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 18379 (2009).
4. J. Scholz, M. C. Klein, T. E. Behrens, H. Johansen-Berg, *Nat. Neurosci.* **12**, 1370 (2009).
5. Supplementary information is available as supporting material on *Science* Online.
6. J. P. Lerch *et al.*, *Neuroimage* **54**, 2086 (2011).
7. D. I. Perrett, J. K. Hietanen, M. W. Oram, P. J. Benson, E. T. Rolls, *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **335**, 23 (1992).
8. M. A. Pinsk *et al.*, *J. Neurophysiol.* **101**, 2581 (2009).
9. D. Y. Tsao, S. Moeller, W. A. Freiwald, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 19514 (2008).
10. Y. Kikuchi, B. Horwitz, M. Mishkin, *J. Neurosci.* **30**, 13021 (2010).
11. R. Zahn *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **104**, 6430 (2007).
12. I. R. Olson, A. Plotzker, Y. Ezzyat, *Brain* **130**, 1718 (2007).
13. A. Izquierdo, R. K. Suda, E. A. Murray, *J. Neurosci.* **25**, 8534 (2005).
14. R. Adolphs, *Annu. Rev. Psychol.* **60**, 693 (2009).
15. T. E. Behrens, L. T. Hunt, M. W. Woolrich, M. F. Rushworth, *Nature* **456**, 245 (2008).
16. C. D. Frith, *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **362**, 671 (2007).
17. R. B. Mars *et al.*, *J. Neurosci.* **31**, 4087 (2011).
18. S. Tsujimoto, A. Genovesio, S. P. Wise, *Trends Cogn. Sci.* **15**, 169 (2011).
19. J. I. Flombaum, L. R. Santos, *Curr. Biol.* **15**, 447 (2005).
20. H. Seo, D. Lee, *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **363**, 3845 (2008).
21. N. Fujii, S. Hihara, Y. Nagasaka, A. Iriki, *Soc. Neurosci.* **4**, 73 (2009).
22. T. E. Behrens, L. T. Hunt, M. F. Rushworth, *Science* **324**, 1160 (2009).
23. J. Moll, R. Zahn, R. de Oliveira-Souza, F. Krueger, J. Grafman, *Nat. Rev. Neurosci.* **6**, 799 (2005).
24. M. D. Lieberman, *Annu. Rev. Psychol.* **58**, 259 (2007).
25. O. Schülke, J. Bhagavatula, L. Vigilant, J. Ostner, *Curr. Biol.* **20**, 2207 (2010).
26. D. Zumpe, R. P. Michael, *Am. J. Primatol.* **10**, 291 (1986).
27. M. Petrides, D. N. Pandya, *J. Neurosci.* **27**, 11573 (2007).
28. P. H. Rudebeck, M. J. Buckley, M. E. Walton, M. F. Rushworth, *Science* **313**, 1310 (2006).
29. H. Barbas, H. Ghashghaei, S. M. Dombrowski, N. L. Rempel-Clower, *J. Comp. Neurol.* **410**, 343 (1999).
30. R. A. Barton, *J. Evol. Biol.* **20**, 1504 (2007).

Acknowledgments: Funded by the UK Medical Research Council and Wellcome Trust (M.P.N., K.M.). We thank C. Bergmann and Biomedical services staff for their assistance and R. Dunbar for helpful discussion.

Supporting Online Material

www.sciencemag.org/cgi/content/full/334/6056/697/DC1
Materials and Methods
SOM Text
Fig. S1
Tables S1 to S5
References and Notes

20 June 2011; accepted 27 September 2011
10.1126/science.1210027

Social Network Size Affects Neural Circuits in Macaques

J. Sallet, R. B. Mars, M. P. Noonan, J. L. Andersson, J. X. O'Reilly, S. Jbabdi, P. L. Croxson, M. Jenkinson, K. L. Miller and M. F. S. Rushworth

Science **334** (6056), 697-700.
DOI: 10.1126/science.1210027