Supplementary Information for

Amygdala Volume and Social Network Size in Humans

Kevin C. Bickart[1], Christopher I. Wright[2], Rebecca J. Dautoff[2], Bradford C. Dickerson[2,3], Lisa Feldman Barrett[2,4]

[1]Department of Anatomy and Neurobiology, Boston University School of Medicine

[2]Psychiatric Neuroimaging Research Program and Martinos Center for Biomedical Imaging, [3]Department of Neurology, Massachusetts General Hospital and Harvard Medical School

[4]Department of Psychology, Northeastern University

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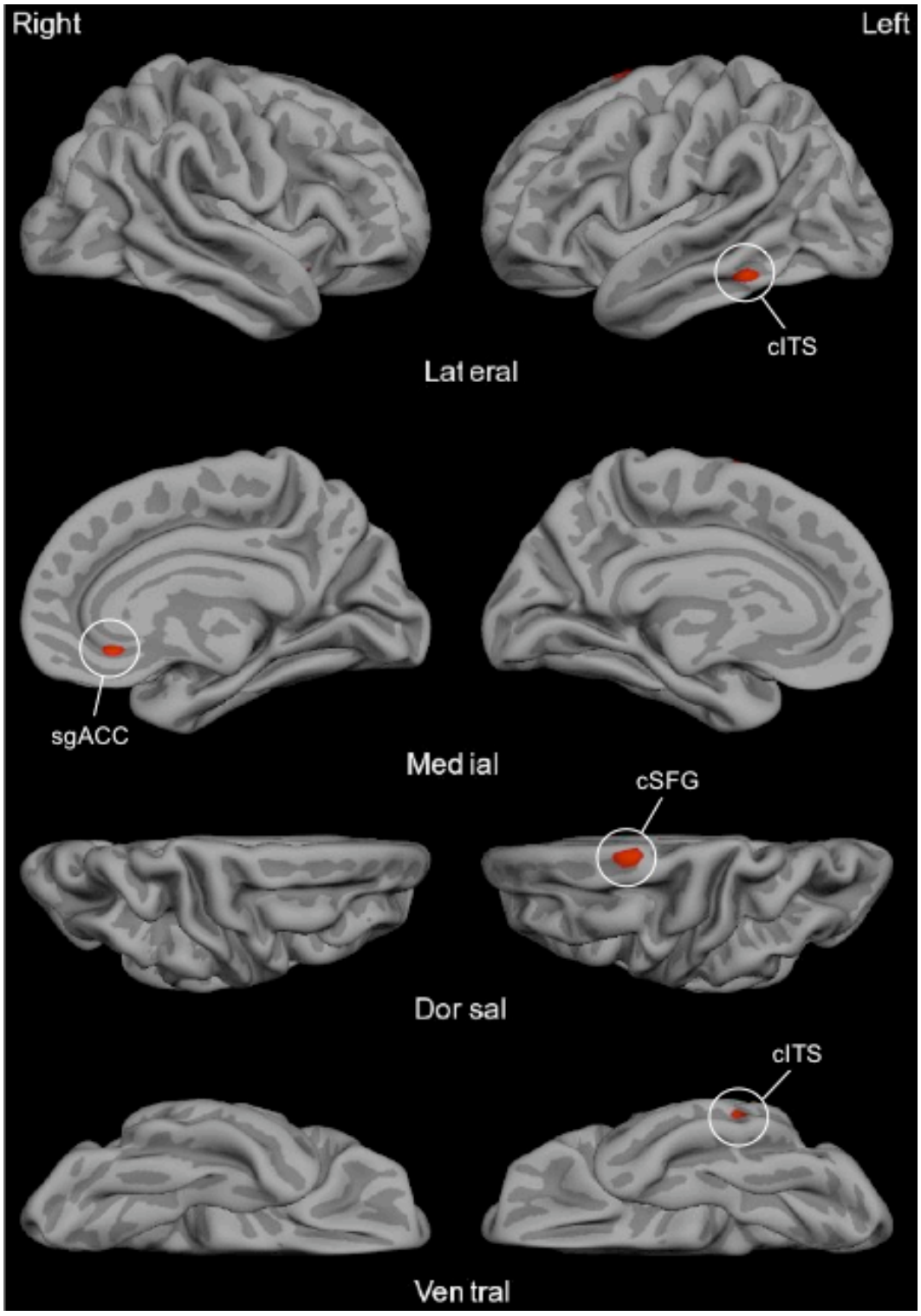
Supplementary Figure 1. Significant correlations of cortical thickness and Social Network Size.



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Supplementary Table 1. Hierarchical linear regressions using amygdala and hippocampal volumes (corrected for total intracranial volume) as independent variables and social network characteristics as dependent variables. Standardized regression coefficients (B), *t* values, and *p* values (2 tailed, in parentheses) are displayed.

	Left amygdala	Left hippocampus	Right amygdala	Right hippocampus
Social Network Size	0.55, 2.51 (0.02)	–0.17, –0.78 (0.44)	0.44, 2.36 (0.02)	–0.14, –0.75 (0.46)
Social Network Complexity	0.57, 2.66 (0.01)	–0.12, –0.57 (0.57)	0.41, 2.28 (0.03)	–0.04, –0.22 (0.83)

Supplementary Table 2. Surface area and peak vertex significance value for ROIs demonstrating significant correlations between cortical thickness and Social Network Size for the whole sample.

Region	Peak p value	Surface area at $p<.01$, uncorrected (mean/sd, in sq mm)
Right Subgenual Anterior Cingulate Cortex	0.0025	3.0 (0.4)
Left Caudal Superior Frontal Gyrus	0.0067	2.9 (0.3)
Left Caudal Inferior Temporal Sulcus	0.0023	2.5 (0.3)

Surface area and peak vertex significance values within these ROIs were similar for both social network variables (Social Network Size and Complexity) and thus we only display those for Social Network Size here. Correlations were thresholded at $p<.01$, uncorrected for multiple comparisons.

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Supplementary Table 3. Correlations between mean cortical thickness and Social Network Size from independent whole brain surface-based analyses for young and older subsamples.

Region	Young	Old
Right Subgenual Anterior Cingulate Cortex	r=0.74; p=0.002	r=0.48; p=0.008
Left Caudal Superior Frontal Gyrus	r=0.34; p=0.02	r=0.46; p=0.01
Left Caudal Inferior Temporal Sulcus	r=0.65; p=0.009	r=0.35; p=0.05

Correlations within these ROIs were similar for both social network variables (Social Network Size and Complexity) and thus we only display those for Social Network Size here. Correlations were thresholded at $p<.01$, uncorrected for multiple comparisons.

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Supplementary Methods

MRI imaging was performed using a Siemens Magnetom Trio Tim 3T whole body high-speed imaging device to collect 2 T1-weighted images with a 3D MPRAGE sequence (TR/TI/TE/flip angle = 2.53s/900ms/3.39ms/7°, FOV = 256, matrix = 240x256, resolution = 1 mm isotropic). The automated segmentation method used in this study employed a manually labeled atlas dataset from 40 individuals to automatically segment and assign neuroanatomic ROI labels to 40 different brain structures (including the amgydala) based on probabilistic estimations. This procedure has been widely used in volumetric studies and was shown to be comparable in accuracy to that of manual labeling[1]. A trained operator, blind to the hypothesis, manually inspected the results of the automated amygdala segmentation. In this analysis, no adjustments, modifications, or edits were made; the results of the automated segmentation were verified as accurate without need for correction. The criteria used for this inspection with regard to the amygdala are an in-house laboratory manual of the boundaries of the amygdala, which were summarized briefly in a previous publication[2].

In addition to the amygdala and hippocampus, Freesurfer (http://surfer.nmr.mgh.harvard.edu) segments the following subcortical structures: the brainstem as well as the right and left accumbens area, ventral diencephalon, thalamus, caudate, putamen, and globus pallidus[1]. As in our primary analysis, we conducted linear regressions using subcortical volumes (corrected for total intracranial volume) as independent variables and social network size and complexity as dependent variables while controlling for age (because these subcortical brain regions typically diminish with age). We performed this analysis for the whole group as well as in the subgroups of

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younger and older participants. Because this was an exploratory analysis, we corrected for multiple comparisons at $p<0.004$ based on a Bonferroni correction.

To assess the discriminant validity of the correlation between amygdala size and social network size and complexity, we also measured participants' reported levels of social support and life satisfaction. We used the Social Provisions Scale[3] to assess perceived availability of social support based on participants' views of their current relationships. The scale consists of 24 items (e.g. "I feel part of a group of people who share my attitudes and beliefs.") rated on a scale from 1 (strongly disagree) to 4 (strongly agree). The Social Provisions Scale provides a summary score as well as a score for 6 provisions of social relationships including guidance (advice or information), reliable alliance (assurance that others can be counted on in times of stress), reassurance of worth (recognition of one's competence), attachment (emotional closeness), social integration (a sense of belonging to a group of friends), and opportunity for nurturance (providing assistance to others). To measure the frequency of receipt of emotional and instrumental support, we used the Perceived Social Network Support[4] assessment adopted from the MacArthur study of successful aging. This assessment consists of 6 items (e.g. "How often do people in your life listen to your worries?") rated on a scale from 0 (never) to 3 (frequently) for each of 4 sources (spouse, children, friends, and relatives), providing a score for each item. We used the Satisfaction with Life Scale[5] to assess participants' global life satisfaction. The scale consists of 5 items (e.g. "So far I have gotten the important things I want in life.") rated on a scale from 1 (strongly agree) to 7 (strongly disagree) and provides an overall life satisfaction score.

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The exploratory morphometric analysis procedures surveying the entire cerebral cortex for cortical thickness-related correlates of variables of interest have been described in detail and applied and demonstrated to be valid and reliable in a number of publications[6-12]. T1-weighted MRI image volumes were processed in a fully automated fashion using a cortical surface-based reconstruction that ultimately provides measurements of cortical thickness throughout the cortical mantle for each individual participant.

Exploratory statistical analysis of the whole cortical mantle was performed using the general linear model[2, 7, 13-15]. Separate models were used for the social network size and complexity variables. In each analysis, the social network variable was the predictor variable, with age and gender as covariates, and cortical thickness was the dependent variable. These analyses were performed for the entire group of participants, and to verify reliability of findings, the analyses were performed again for younger and older participants separately. Because our goal was to explore the entire cortex for subtle effects of interest related to the social network variables, we used a relatively liberal statistical threshold, $p<0.01$, uncorrected for multiple comparisons.

Supplementary Results

For the whole group, linear regression analyses, controlling for age, revealed no significant relationships between the additional subcortical volumes (corrected for total intracranial volume) and social network characteristics at $p<0.004$, corrected for multiple comparisons. For the younger and older subsamples, linear regression analyses again revealed no significant relationships between the additional subcortical volumes

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(corrected for total intracranial volume) and social network characteristics at $p<0.004$, corrected for multiple comparisons. At a more liberal statistical threshold of $p<0.05$, left nucleus accumbens volume (corrected for total intracranial volume) predicted social network size and complexity in the whole-group analysis (B = 0.35, $t = 2.65$, $p = 0.01$ for social network complexity; B = 0.29, $t = 2.09$, $p = 0.04$ for social network size) and predicted social network complexity in the younger adults (B = 0.48, $t = 2.28$, $p = 0.036$), whereas right putamen and right globus pallidus volumes (corrected for total intracranial volume) significantly predicted social network complexity in the older adults (B = 0.37, $t = 2.44$, $p = 0.02$; B = 0.39, $t = 2.57$, $p = 0.01$, respectively). These findings should be interpreted with caution as they were not hypothesized a priori nor detected at the a priori-specified statistical threshold for the exploratory analysis.

Although the two social network variables were highly correlated and therefore shared the majority of their reliable variance, we examined whether amygdala volumes predicted the small amount of unique variance in each social network variable. We conducted hierarchical linear regressions. We found that the total relation between social network size and amygdala was significantly larger than what would be expected by chance (B = .38, $t = 3.11$, $p < .003$), as reported in the main manuscript, but the small amount of additional variance that was unique only to social network size (not shared with social network complexity) was not predicted by amygdala volume (B = .03, $t = .12$, $p = .91$). Similarly, the total relation between social network complexity and amygdala was significantly greater than what would be expected by chance (B = .44, $t = 3.7$, $p < .001$), as reported in the main manuscript, but the small amount of additional variance that was unique only to social network complexity (not shared with social network size)

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was only marginally predicted by amygdala volume (B = .42, t = 1.8, p = .08). This pattern of findings indicates that most of the variance predicted by amygdala volume was shared by the two social network measures. The amygdala seems to be related to what these measures share in common, which, given their strong correlation, was most of their reliable variance.

The cortical thickness of three areas was correlated with both social network variables (Size and Complexity): the left caudal inferior temporal sulcus (cITS: MNI coordinates -59, -42, -17), left caudal superior frontal gyrus (cSFG: MNI -10, 6, 67), right subgenual anterior cingulate cortex (sgACC: MNI 8, 29, -8), p<0.01, uncorrected for multiple comparisons. Supplementary Figure 1 displays a colorized statistical map superimposed upon a partially inflated group average cortical surface. The lateral, medial, dorsal, and ventral aspects of the right and left hemispheres are shown. Supplementary Table 2 displays surface area and peak vertex significance for ROIs demonstrating significant correlations between cortical thickness and Social Network Size for the entire sample. Results were almost identical for both social network variables, thus we only display correlations for Social Network Size in Supplementary Figure 1 and Table 2.

Furthermore, we performed an additional analysis to demonstrate that our findings were not due to chance. We ran separate exploratory whole-cortex analyses (in the same fashion as described above for the entire sample) in the subsample of younger adults (19-32 years of age) and in the subsample of older adults (46-83 years of age). Each of these two analyses produced regions of interest (ROIs), which overlapped substantially across the subsamples and with the ROIs produced by the whole group analysis, and therefore we defined regions of interest based on these three regions from

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each separate subsample, mapped them to each individual, and extracted thickness values for each subject. The results show very similar correlations, as shown in Supplementary Table 3, for these ROIs in the young and in the older adults. This is a replication of the results in two samples that are independent from one another (although not independent from the whole group analysis) providing strong evidence that the findings in these areas are not due to chance. There were some additional areas observed in each individual subsample but these regions were considered as likely false positive regions since they were identified with a liberal threshold, did not overlap across the two subsamples, and were not seen in the original larger analysis of the entire group.

Supplementary Discussion

Findings from our study provoke the question, "Is a bigger amygdala better?" To answer this question, we must consider what "bigger" means and what a bigger amygdala might be "better" for. Striedter[16] suggests that bigger means better connected, so that a brain region with more volume (in cross-species or within species comparisons) has an enhanced ability to modulate processing in its target regions. From cross-species comparisons in nonhuman primates, researchers propose that a bigger amygdala might provide processing advantages for visual signals from conspecifics (cf[17, 18]). In the context of our findings, Striedter's "large equals well-connected" rule suggests that humans with a larger amygdala with denser connectivity might be better equipped to seek out, learn about, and coordinate appropriate neural and behavioral responses to

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multifaceted visual information that allows people to develop and maintain a larger, more complex social network.

In humans, much of social communication occurs via the visual modality, and from neuroimaging research, it is apparent that the amygdala plays a particularly important role in processing of identity[18, 19], trustworthiness[20-23], and all visual signals that involve some degree of uncertainty, ambiguity, or novelty[24-31]. Yet it is far from clear that the cross-species comparisons can be generalized to infer that a bigger amygdala is better in humans, particularly when it comes to social functioning.

There are few existing studies to assess the relation between amygdala volume and social functioning, and most of the existing studies focus on patients with autism. Thus far, amygdala volume is not systematically related to social adjustment in these individuals. Using structural MRI, studies found that young children with autism have significantly larger amygdalae than age-matched controls[32, 33, 34]. Other studies examining older adolescents and young adults found no difference in[35-37] or even significantly smaller[38-40] amygdala volumes in individuals with autism as compared to age-matched controls. These findings suggest that the amygdala undergoes abnormal development in the life of an autistic individual, with larger amygdalae in early childhood and smaller amygdalae in later adolescence and adulthood (cf[34]). Furthermore, both larger[33, 34] and smaller[39] amygdala volumes within autistic individuals predicted social impairment. For young children with autism (but not controls), a larger amygdala predicted social and communication impairment[33, 34], whereas, for older adolescents and adults with autism (but again, not controls), a smaller amygdala predicted higher levels of impairment in emotion perception, social reciprocity and nonverbal communication[39]. Individuals

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diagnosed with psychopathy/antisocial personality had significantly smaller amygdalae (left, 17.1%; right, 18.9%) when compared to healthy controls[41] which was most correlated with the affective and interpersonal facets of their disorder.

In healthy humans, the relationship between amygdala volume and socially relevant personality traits is equally unclear. In both healthy young[2] and elderly[15] adults, amygdala volumes did not correlate with social behavior as indexed by self-reports of extraversion on the NEO Five-Factor Inventory. Elderly participants who described themselves as higher in agreeableness displayed a trend to have larger amygdala volumes (corrected for gender and age)[15].

From the existing structural neuroimaging work in humans, then, it remains unclear whether a bigger amygdala is better for social functioning. Nevertheless, the hypothesis that a bigger amygdala is better equipped to handle more social information from more people in more social contexts has never been directly studied and our findings provoke an interesting question for future research on the role of the amygdala in the social brain.

References

1. Fischl, B.*, et al.* Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* **33**, 341-355 (2002).

2. Wright, C.I.*, et al.* Neuroanatomical correlates of extraversion and neuroticism. *Cereb Cortex* **16**, 1809-1819 (2006).

3. Russell, D., Cutrona, C.E., Rose, J. & Yurko, K. Social and emotional loneliness: an examination of Weiss's typology of loneliness. *J Pers Soc Psychol* **46**, 1313-1321 (1984).

4. Gurung, R.A.R., Taylor, S.E. & Seeman, T.E. Accounting for changes in social support among married older adults: Insights from the MacArthur studies of successful aging. *Psychology and Aging* **18**, 487-496 (2003).

5. Diener, E., Emmons, R.A., Larsen, R.J. & Griffin, S. The Satisfaction with Life Scale. *Journal of Personality Assessment* **49**, 71-75 (1985).

6. Dale, A.M., Fischl, B. & Sereno, M.I. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* **9**, 179-194 (1999).

7. Dickerson, B.C.*, et al.* Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths. *Neuroimage* **39**, 10-18 (2008).

8. Fischl, B. & Dale, A.M. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America* **97**, 11050-11055 (2000).

9. Fischl, B., Sereno, M.I. & Dale, A.M. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage* **9**, 195-207 (1999).

10. Fischl, B., Sereno, M.I., Tootell, R.B. & Dale, A.M. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp* **8**, 272-284 (1999).

11. Han, X.*, et al.* Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. *Neuroimage* **32**, 180-194 (2006).

12. Rosas, H.D.*, et al.* Evidence for more widespread cerebral pathology in early HD: an MRI-based morphometric analysis. *Neurology* **60**, 1615-1620 (2003).

13. Bakkour, A., Morris, J.C. & Dickerson, B.C. The cortical signature of prodromal AD: regional thinning predicts mild AD dementia. *Neurology* **72**, 1048-1055 (2009).

14. Dickerson, B.C.*, et al.* The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex* **19**, 497-510 (2009).

Nature Neuroscience: doi:10.1038/nn.2724

15. Wright, C.I., Feczko, E., Dickerson, B. & Williams, D. Neuroanatomical correlates of personality in the elderly. *Neuroimage* **35**, 263-272 (2007).

16. Striedter, G.F. *Principles of Brain Evolution* (Sunderland, 2005).

17. Barton, R.A. & Aggleton, J.P. Primate evolution and the amygdala. in *The amygdala: a functional analysis* (ed. J.P. Aggleton) 480-508 (2000).

18. Pourtois, G., Schwartz, S., Seghier, M.L., Lazeyras, F. & Vuilleumier, P. View-independent coding of face identity in frontal and temporal cortices is modulated by familiarity: an event-related fMRI study. *Neuroimage* **24**, 1214-1224 (2005).

19. Schwartz, C.E*., et al.* Differential amygdalar response to novel versus newly familiar neutral faces: a functional MRI probe developed for studying inhibited temperament. *Biol Psychiatry* **53**, 854-862 (2003).

20. Winston, J.S., Strange, B.A., O'Doherty, J. & Dolan, R.J. Automatic and intentional brain responses during evaluation of trustworthiness of faces. *Nat Neurosci* **5**, 277-283 (2002).

21. Said, C.P., Baron, S.G. & Todorov, A. Nonlinear amygdala response to face trustworthiness: contributions of high and low spatial frequency information. *J Cogn Neurosci* **21**, 519-528 (2009).

22. Engell, A.D., Haxby, J.V. & Todorov, A. Implicit trustworthiness decisions: automatic coding of face properties in the human amygdala. *J Cogn Neurosci* **19**, 1508-1519 (2007).

23. Todorov, A. & Engell, A.D. The role of the amygdala in implicit evaluation of emotionally neutral faces. *Soc Cogn Affect Neurosci* **3**, 303-312 (2008).

24. Weierich, M.R., Wright, C.I., Negreira, A., Dickerson, B.C. & Barrett, L.F. Novelty as a dimension in the affective brain. *Neuroimage* **49**, 2871-2878 (2010).

25. Herry, C*., et al.* Processing of temporal unpredictability in human and animal amygdala. *J Neurosci* **27**, 5958-5966 (2007).

26. Hsu, M., Bhatt, M., Adolphs, R., Tranel, D. & Camerer, C.F. Neural systems responding to degrees of uncertainty in human decision-making. *Science* **310**, 1680-1683 (2005).

27. Davis, M. & Whalen, P.J. The amygdala: vigilance and emotion. *Mol Psychiatry* **6**, 13-34 (2001).

Nature Neuroscience: doi:10.1038/nn.2724

28. Whalen, P.J. The uncertainty of it all. *Trends Cogn Sci* **11**, 499-500 (2007).

29. Wright, C.I.*, et al.* Neural correlates of novelty and face-age effects in young and elderly adults. *Neuroimage* **42**, 956-968 (2008).

30. Wright, C.I.*, et al.* Novelty responses and differential effects of order in the amygdala, substantia innominata, and inferior temporal cortex. *Neuroimage* **18**, 660-669 (2003).

31. Moriguchi, Y.*, et al.* Differential Hemodynamic Response in Affective Circuitry with Aging: An fMRI Study of Novelty, Valence, and Arousal. *J Cogn Neurosci* (in press).

32. Mosconi, M.W.*, et al.* Longitudinal study of amygdala volume and joint attention in 2- to 4-year-old children with autism. *Arch Gen Psychiatry* **66**, 509-516 (2009).

33. Sparks, B.F.*, et al.* Brain structural abnormalities in young children with autism spectrum disorder. *Neurology* **59**, 184-192 (2002).

34. Schumann, C.M., Barnes, C.C., Lord, C. & Courchesne, E. Amygdala enlargement in toddlers with autism related to severity of social and communication impairments. *Biol Psychiatry* **66**, 942-949 (2009).

35. Schumann, C.M.*, et al.* The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. *J Neurosci* **24**, 6392-6401 (2004).

36. Palmen, S.J., Durston, S., Nederveen, H. & Van Engeland, H. No evidence for preferential involvement of medial temporal lobe structures in high-functioning autism. *Psychol Med* **36**, 827-834 (2006).

37. Haznedar, M.M.*, et al.* Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. *Am J Psychiatry* **157**, 1994-2001 (2000).

38. Aylward, E.H.*, et al.* MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. *Neurology* **53**, 2145-2150 (1999).

39. Nacewicz, B.M.*, et al.* Amygdala volume and nonverbal social impairment in adolescent and adult males with autism. *Arch Gen Psychiatry* **63**, 1417-1428 (2006).

40. Pierce, K., Muller, R.A., Ambrose, J., Allen, G. & Courchesne, E. Face processing occurs outside the fusiform 'face area' in autism: evidence from functional MRI. *Brain* **124**, 2059-2073 (2001).

Nature Neuroscience: doi:10.1038/nn.2724

41. Yang, Y., Raine, A., Narr, K.L., Colletti, P. & Toga, A.W. Localization of deformations within the amygdala in individuals with psychopathy. *Arch Gen Psychiatry* **66**, 986-994 (2009).

Nature Neuroscience: doi:10.1038/nn.2724