typically measured in single-molecule force-extension curves). For example, suppose that each base step can adopt either a short or a long conformation (say 3.3 Å ± 10%) of equivalent energy, and that the conformational state of contiguous bases is correlated over a length of 35 nucleotides. In the absence of tension, short DNA duplexes would populate equally the short and long conformations and therefore exhibit end-to-end distance distributions covering ±10% of the mean length (Fig. 4). The variance of these distributions would grow quadratically with duplex length (24). Under a stretching force, however, the DNA would preferentially adopt the long conformation, and this degree of freedom would saturate at modest tensions. At room temperature, 99% of the base steps would exist in the long conformation under 8 pN of applied force, and the apparent stretching modulus would be 1000 pN (24). Thus, a very soft stretching degree of freedom in the absence of tension can behave as a very stiff stretching degree of freedom when the duplex is under tension. The stretching of DNA at larger forces would presumably occur by a different mechanism. We note that this two-state model is oversimplified with respect to our data because our measurements would spatially resolve the short and long states if only two existed. However, the saturation behavior holds for models with a larger number of states.

Additional theoretical and experimental work will be required to reveal the microscopic basis for correlated DNA stretching fluctuations and its potential relation to other recently discovered nonideal properties of DNA (8–10). Whereas FRET experiments with nanosecond time resolution indicate large DNA stretching fluctuations (25), alternative FRET experiments that average single-molecule FRET signals over hundreds of microseconds do not (27). Thus, DNA stretching dynamics likely occur on a time scale between 10^{-8} and 10^{-5} s. Molecular simulations intended to model DNA stretching will have to access this time regime.

The presence of long-range stretching correlations implies that DNA double helices can, in principle, transmit information over at least 20 bp through an allosteric "domino effect" (28, 29). For example, in the context of the two-state model, a protein that favors binding to a stretched segment of double helix would disfavor the binding of another protein that prefers a compressed conformation. This effect would propagate to sites within 20 bp, and possibly farther. Whether such DNA-mediated allosteric communication alters how the double helix and its specific binding partners interact to regulate biological processes remains to be tested.

References and Notes

1. J. D. Watson, F. H. Crick, *Nature* **171**, 737 (1953).
2. Z. Bryant *et al.*, *Nature* **424**, 338 (2003).
3. S. B. Smith, Y. Cui, C. Bustamante, *Science* **271**, 795 (1996).
4. D. Shore, R. L. Baldwin, *J. Mol. Biol.* **170**, 957 (1983).
5. D. Shore, R. L. Baldwin, *J. Mol. Biol.* **170**, 983 (1983).
6. M. D. Wang, H. Yin, R. Landick, J. Gelles, S. M. Block, *Biophys. J.* **72**, 1335 (1997).
7. D. E. Depew, J. C. Wang, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 4275 (1975).
8. J. Gore *et al.*, *Nature* **442**, 836 (2006).
9. T. E. Cloutier, J. Widom, *Mol. Cell* **14**, 355 (2004).
10. T. E. Cloutier, J. Widom, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 3645 (2005).
11. A. Hillisch, M. Lorenz, S. Diekmann, *Curr. Opin. Struct. Biol.* **11**, 201 (2001).
12. C. Sönnichsen, B. M. Reinhard, J. Liphardt, A. P. Alivisatos, *Nat. Biotechnol.* **23**, 741 (2005).
13. P. Zhu, J. P. Clamme, A. A. Deniz, *Biophys. J.* **89**, L37 (2005).
14. L. S. Churchman, Z. Okten, R. S. Rock, J. F. Dawson, J. A. Spudich, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 1419 (2005).
15. P. A. B. Harbury, *PLoS ONE* **3**, e3229 (2008).
16. W. K. Olson, A. A. Gorin, X. J. Lu, L. M. Hock, V. B. Zhurkin, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 11163 (1998).
17. J. D. Griffith, *Science* **201**, 525 (1978).
18. C. Rivetti, M. Guthold, C. Bustamante, *J. Mol. Biol.* **264**, 919 (1996).
19. K. Sakata-Sogawa, M. Kurachi, K. Sogawa, Y. Fujii-Kuriyama, H. Tashiro, *Eur. Biophys. J.* **27**, 55 (1998).
20. S. B. Zimmerman, B. H. Pheiffer, *J. Mol. Biol.* **135**, 1023 (1979).
21. N. B. Ulyanov, T. L. James, *Methods Enzymol.* **261**, 90 (1995).
22. C. G. Baumann, S. B. Smith, V. A. Bloomfield, C. Bustamante, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 6185 (1997).
23. J. M. Schurr, B. S. Fujimoto, *Biopolymers* **54**, 561 (2000).
24. See supporting material on *Science* Online.
25. T. A. Laurence, X. Kong, M. Jager, S. Weiss, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 17348 (2005).
26. Q. Cai *et al.*, *Nucleic Acids Res.* **34**, 4722 (2006).
27. E. Nir *et al.*, *J. Phys. Chem. B* **110**, 22103 (2006).
28. J. M. Schurr, J. J. Delrow, B. S. Fujimoto, A. S. Benight, *Biopolymers* **44**, 283 (1997).
29. K. M. Kosikov, A. A. Gorin, V. B. Zhurkin, W. K. Olson, *J. Mol. Biol.* **289**, 1301 (1999).
30. A. V. Morozov, J. J. Havranek, D. Baker, E. D. Siggia, *Nucleic Acids Res.* **33**, 5781 (2005).
31. Y. Liu, D. L. Beveridge, *J. Biomol. Struct. Dyn.* **18**, 505 (2001).
32. T. D. Fenn, D. Ringe, G. A. Petsko, *J. Appl. Crystallogr.* **36**, 944 (2003).
33. We thank C. J. Ackerson for discussions on nanocrystal synthesis; R. L. Baldwin, F. E. Boas, Z. D. Bryant, L. S. Churchman, A. R. Dunn, D. R. Halpin, D. Herschlag, W. L. Martin, B. H. Robinson, J. M. Schurr, A. L. Smith, R. M. Weisinger, and S. J. Wrenn for insights into DNA; Y. Bai, S. Doniach, K. Ito, J. Lipfert, I. S. Millett, S. Seifert, P. Thiyagarajan and H. Tsuruta for assistance and advice on x-ray scattering; T. D. Fenn for writing code that was used to calculate crystallographic dispersion values and for valuable discussions throughout this work; P. A. Walker for expert assistance with DNA synthesis; and P. Bradley and D. Baker for permitting use of unpublished code to prepare Fig. 4. Supported by NIH grants GM068126-01 and DP OD000429-01 (P.A.B.H.), an NIH training grant fellowship (R.S.F.), an NSF graduate fellowship (R.D.), and the U.S. Department of Energy (contract W-31-109 Eng-438 to the Advanced Photon Source, and support of Stanford Synchrotron Radiation Laboratory).

Relation Between Obesity and Blunted Striatal Response to Food Is Moderated by *Taq*IA A1 Allele

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The dorsal striatum plays a role in consummatory food reward, and striatal dopamine receptors are reduced in obese individuals, relative to lean individuals, which suggests that the striatum and dopaminergic signaling in the striatum may contribute to the development of obesity. Thus, we tested whether striatal activation in response to food intake is related to current and future increases in body mass and whether these relations are moderated by the presence of the A1 allele of the *Taq*IA restriction fragment length polymorphism, which is associated with dopamine D2 receptor (*DRD2*) gene binding in the striatum and compromised striatal dopamine signaling. Cross-sectional and prospective data from two functional magnetic resonance imaging studies support these hypotheses, which implies that individuals may overeat to compensate for a hypofunctioning dorsal striatum, particularly those with genetic polymorphisms thought to attenuate dopamine signaling in this region.

Although twin studies suggest that biological factors play a major role in the etiology of obesity, few prospective studies have identified biological factors that increase risk for future weight gain. Dopamine is involved in the reinforcing effects of food (1). Feeding is associated with dopamine release in the dorsal striatum, and the degree of pleasure from eating correlates with amount of dopamine release (2, 3). The dorsal striatum responds to

ingestion of chocolate in lean humans and is sensitive to its devaluation by feeding beyond satiety (4). In contrast, the ventral striatum appears to respond to food receipt only if it is unexpected (5) and plays a preferential role in encoding the value of cues associated with food receipt, reacting preferentially to cues versus receipt (6) and showing sensitivity to the devaluation of food cues, but not food receipt (4, 7). Thus, the dorsal and ventral striatum may serve distinct roles in encoding food reward, with the former playing a more prominent role in encoding consummatory food reward. Dopamine antagonists increase appetite, energy intake, and weight gain, whereas dopamine agonists reduce energy intake and produce weight loss (8, 9). Dopamine D2 receptors are reduced in obese relative to lean individuals (10, 11). Obese rats have lower basal dopamine levels and reduced D2 receptor expression compared with lean rats (12, 13). It has therefore been postulated that obese individuals have hypofunctioning reward circuitry, which leads them to overeat to compensate for a hypofunctioning dopamine reward system (14).

We used blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (fMRI) to test whether obese, relative to lean, individuals show abnormal activation of the dorsal striatum, which encodes consummatory food reward (2, 4), in response to receiving a highly palatable food. Although BOLD response reflects blood flow, and not dopamine signaling, it has been argued that the BOLD signal in regions that register as a dopamine source or target probably reflects dopaminergic activity (15–17). In addition, in genetically homogeneous and heterogeneous samples, individuals with an A1/A1 or A1/A2 allele of the TaqIA (rs1800497) are more likely to be obese than those without this allele (18–20). Furthermore, six post mortem and positron emission tomography (PET) studies have found that individuals with at least one A1 allele of the TaqIA restriction fragment length polymorphism associated with the dopamine D2 receptor (DRD2) gene evidenced 30 to 40% fewer D2 receptors than those with the A2/A2 allele (21–26), which suggests that reduced D2 receptor availability in obese individuals may be related to this polymorphism. The one study in which this effect did not emerge used single-photon emission computed tomography (SPECT) (27), which implies that SPECT may not be sufficiently sensitive to detect this difference (28). Thus, we further hypothesized that any evidence

of abnormal striatal activation in response to food receipt for obese, relative to lean, individuals would be amplified among those with the A1 allele.

In two fMRI studies, we investigated striatal activation in response to receiving a chocolate milkshake versus a tasteless solution (29). Tastes were delivered using programmable syringe
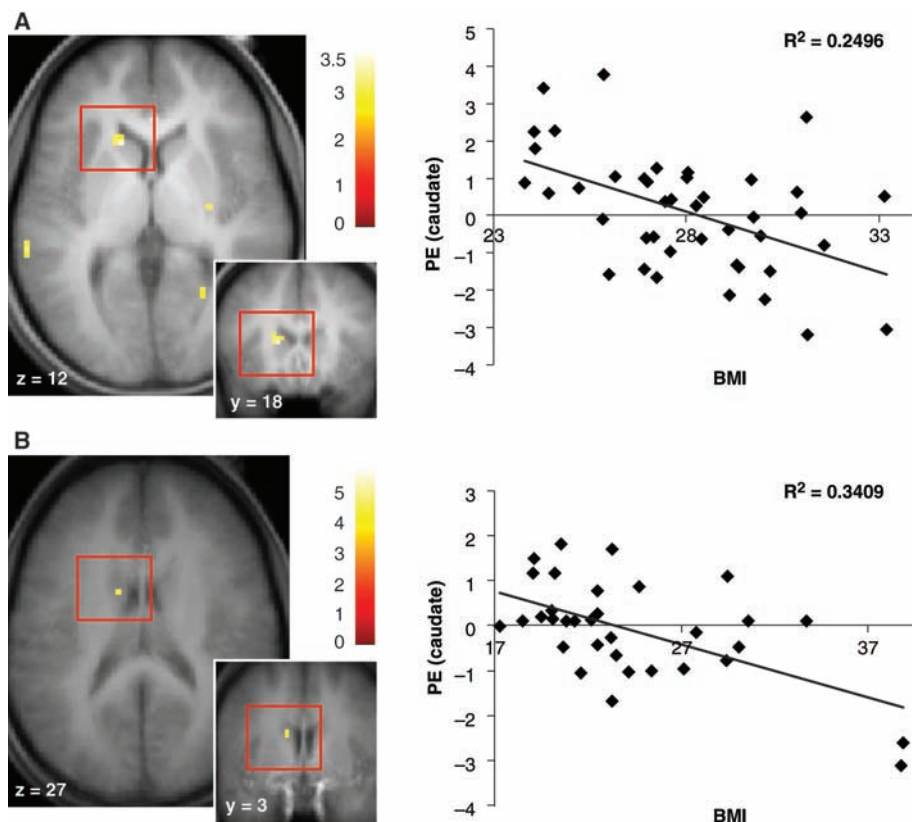

Fig. 1. (A) Coronal section of weaker activation in the left caudate nucleus (−15, 18, 12, t = 3.65, P < 0.05 FDR corrected) in response to receiving a milkshake versus a tasteless solution as a function of BMI with the graph of parameter estimates from that region (study 1). **(B)** Coronal section of weaker activation in the left caudate nucleus (−12, 3, 27, t = 4.00, P < 0.05 FDR corrected) in response to receiving a milkshake versus a tasteless solution as a function of BMI with the graph of parameter estimates from that region (study 2).
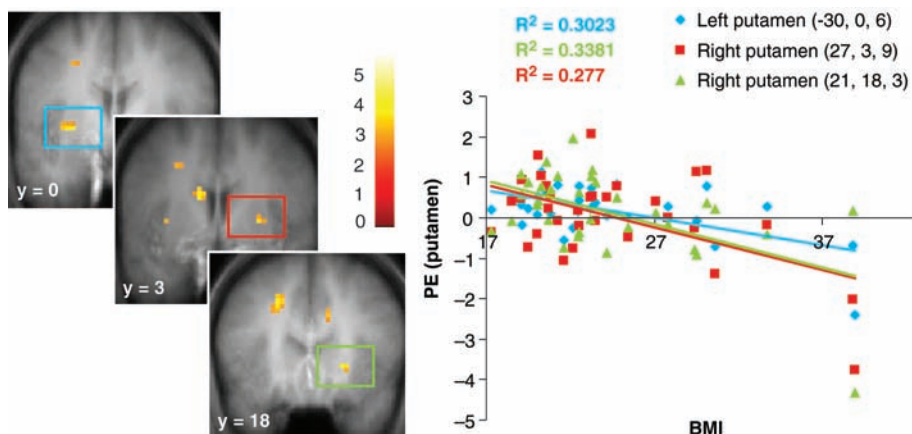

Fig. 2. Coronal section of weaker activation bilaterally in the putamen (−30, 0, 6, t = 3.98, P < 0.05 FDR corrected; 27, 3, 9, t = 3.45, P < 0.05 FDR corrected) in response to milkshake receipt versus tasteless solution receipt as a function of BMI with the graph of parameter estimates from that region (study 2).

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pumps to ensure consistent volume, rate, and timing of taste delivery. This procedure has been used successfully in previous studies (6).

In study 1, 43 female college students (mean age = 20.4, range 18 to 22; mean body mass index (BMI) = 28.60; range 23.8 to 33.2) were scanned while viewing pictures of a glass of chocolate milkshake and a glass of water that predicted taste delivery and while they tasted the milkshake and tasteless solution. The paradigm used in study 2 was similar, but the cues were geometric shapes (diamond, square, or circle) rather than pictures of glasses of milkshake or water. Study 2 involved 33 adolescent girls (mean age = 15.7, range 14 to 18 years; mean BMI = 24.3; range 17.5 to 38.9). Genetic data were obtained from 27 of these 33 participants. Because our hypothesis focused on dorsal striatal involvement in consummatory food reward, analyses focused on response to receiving a milkshake or a tasteless solution, not on response to cues signaling impending receipt of these tastes.

Individual statistical parametric mapping (SPM) contrast maps were entered into regression models with BMI scores as a covariate. In all analyses, t-maps (voxelwise levels of significance) were set at a threshold of $P < 0.005$ with a minimum cluster criterion of three. We then performed region-of-interest searches using peaks in the dorsal striatum identified previously (2, 4) as centroids to define 10-mm diameter spheres. Peaks within these regions were considered significant at $P < 0.05$, false-discovery rate (FDR) corrected across the small volume.

We found a negative correlation between BMI and response in the left caudate nucleus to receiving a milkshake versus a tasteless solution in study 1 ($r = -0.50$) (Fig. 1A) and in study 2 ($r = -0.58$) (Fig. 1B). We also found a negative correlation between BMI and response bilaterally in the putamen to receiving a milkshake versus a tasteless solution in study 2 ($r = -0.53, -0.58$) (Fig. 2). In study 1, presence of the A1 allele significantly moderated the negative relation between BMI and activation in the left caudate while receiving a milkshake versus a tasteless solution ($r = -54$, $P < 0.001$); activation in this region showed a strong inverse relation ($r = -0.83$) to BMI for
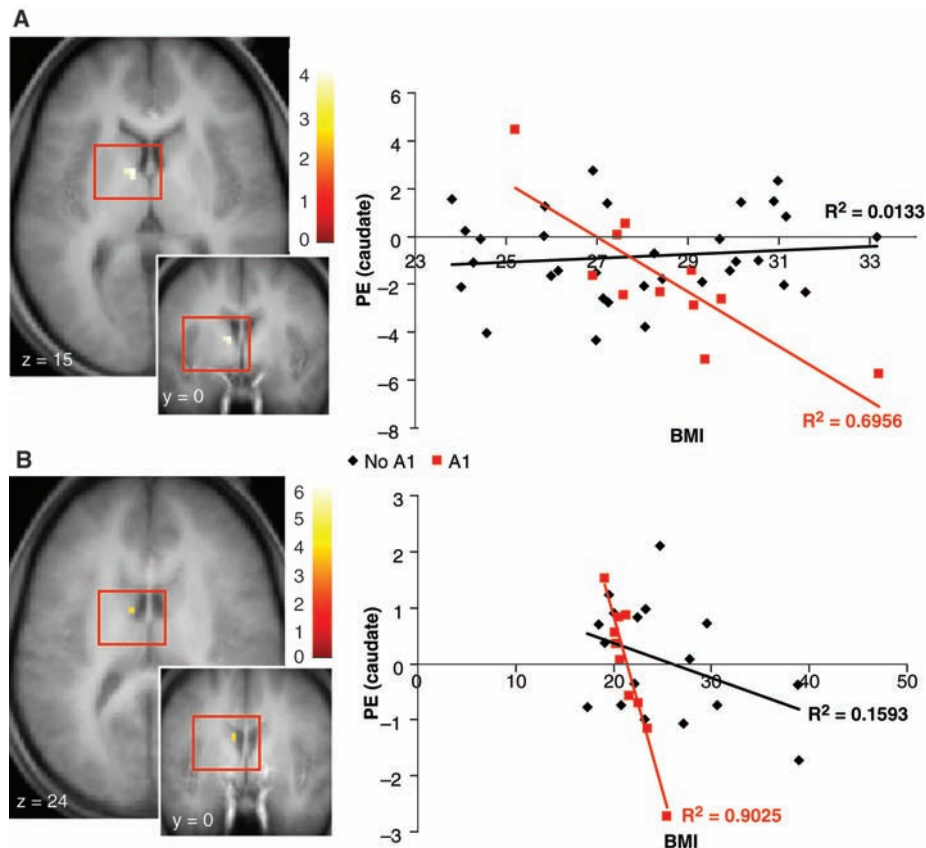

Fig. 3. (**A**) Sagittal section of weaker activation in the left caudate nucleus (−12, −3, 24, $t = 4.00$, $P < 0.05$ FDR corrected; −9, 0, 15, $t = 4.00$, $P < 0.05$ FDR corrected) while receiving a milkshake versus a tasteless solution as a function of BMI depending upon A1 allele status. The graph shows the parameter estimates of the contrast (milkshake receipt versus tasteless solution receipt) across BMI scores for each DRD2 allele type (study 1). (**B**) Coronal section of weaker activation in the left caudate nucleus (−9, 0, 24, $t = 3.81$, $P < 0.05$ FDR corrected) while receiving a milkshake versus a tasteless solution across BMI scores for each DRD2 allele type, with the graph showing the parameter estimates of the contrast (milkshake receipt versus tasteless solution receipt) versus BMI for each allele type (study 2).
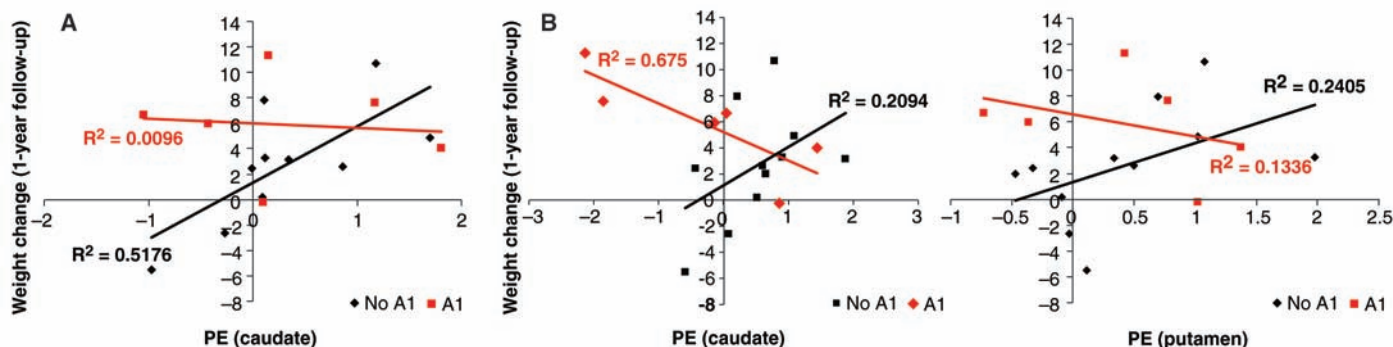

Fig. 4. (**A**) Activation in the caudate nucleus (−12, 3, 27) was negatively related to future weight gain for participants with the A1 allele, but positively related to future weight gain for participants without the A1 allele (study 1). (**B**) Activation in the caudate (6, 9, 15) and putamen (21, 18, 3) was negatively related to future weight gain for participants with the A1 allele, but positively related to future weight gain for participants without the A1 allele (study 2). Note that the graph generated from the caudate peak (left) showed the strongest interaction but just missed significance in the main SPM analysis ($t = 3.0$, $P = 0.002$ uncorrected).

those with the A1 allele, but a weak relation ($r = 0.12$) to BMI for those without this allele (Fig. 3A). In study 2, the A1 allele significantly moderated the negative relation between BMI and activation in the left caudate nucleus during receipt of milkshake versus a tasteless solution ($r = –0.68$, $P < 0.001$); activation in this region showed a strong inverse relation ($r = –0.95$) to BMI for those with the A1 allele, but a weaker relation ($r = –0.40$) to BMI for those without this allele (Fig. 3B). Note that participants with, rather than without, the A1 allele did not differ in their ratings of milkshake pleasantness ($r = 0.16$). Thus, as hypothesized, in both studies obese individuals, relative to lean individuals, showed a blunted striatal response to milkshake receipt, and this effect was amplified in those with the A1 allele.

In study 2, multiple regression models [Statistical Package for the Social Sciences (SPSS)] tested whether presence of the A1 allele moderated the relation between blunted dorsal striatal activation and future increases in BMI (from an increased positive energy balance) over a 1-year follow-up ($n = 17$, mean BMI percent change, 3.63, range –5.5 to 11.3). We controlled for initial BMI, A1 allele status, and dorsal striatal activation. Analyses were performed using the parameter estimates from the most significant peaks from the cross-sectional analyses of study 2. The interaction between A1 status and activation in the right putamen ($r = –0.45$, $P = 0.01$) and activation in the left caudate ($r = –0.42$, $P = 0.02$) while receiving a milkshake versus a tasteless solution in relation to change in BMI were significant and medium in magnitude (Fig. 4). Activation in the putamen ($r = 0.19$) and caudate ($r = 0.26$) and A1 allele status ($r = 0.30$) did not show significant main effects in the prediction of increases in BMI over follow-up.

Collectively, results from these two studies are consistent with the hypothesis that the dorsal striatum is less responsive to food reward in obese, relative to lean, individuals, potentially because the former have reduced D2 receptor density and compromised dopamine signaling, which may prompt them to overeat in an effort to compensate for this reward deficit. We did not observe effects (positive or negative) in the ventral striatum or midbrain, even when we reduced the significance threshold. Because we measured BOLD response, we can only speculate that the effects reflect reduced dopaminergic signaling. However, this interpretation seems reasonable because the presence of the A1 allele, which has been associated with reduced dopaminergic signaling in six studies (21–26), significantly moderated the observed BOLD effects, and because prior work has found that this region shows increased blood flow and increased dopamine release in response to ingestion of palatable food (2, 4). Our findings converge with evidence that obese, relative to

lean, humans have fewer D2 receptors in the striatum (10, 11), and obese, relative to lean, rats have lower basal dopamine levels and reduced D2 receptor density (12, 13). Our findings extend these results by showing that response in the dorsal striatum is blunted during ingestion of palatable food. Our findings also extend work implicating the A1 allele in obesity (30) by providing evidence that the negative relation between striatal response to food receipt and BMI was significantly stronger for individuals with the A1 allele, presumably because these individuals have reduced dopamine signaling capacity in the striatum. Most important, although striatal activation in response to food intake was positively related to weight gain for those without the A1 allele, it was negatively related to weight gain for those with the A1 allele, which provides evidence that blunted dorsal striatal response to food intake temporally precedes weight gain for those with this allele. This finding is consistent with the theory that it represents a vulnerability factor for obesity (31). However, an important alternative explanation to consider is that the hypofunctioning dopamine system results from down-regulation of reward circuitry secondary to overconsumption of high-fat and high-sugar foods (31, 32). Indeed, animal studies indicate that chronic excessive intake of such foods results in down-regulation of postsynaptic D2 receptors, increased D1 receptor binding, and decreased D2 sensitivity and μ-opioid receptor binding (32–34)—changes that also occur in response to chronic substance use. Although we controlled for initial BMI in our prospective analyses, which reduces the risk that a history of overeating explains the prospective effects, we cannot rule out the possibility that the blunted striatal response is caused by overeating, particularly among individuals with the A1 allele. Paradoxically, such an adaptation may further increase the risk for the persistence of overeating.

One cautionary note is that, although studies suggesting that obesity is related to striatal hypofunctioning have included both women and men (10, 11, 14) and obesity is equally prevalent for the two genders, our result should be generalized to males with caution, because we only studied females. Moreover, the evidence that hypofunctioning of the striatum and the A1 allele of *Taq*I are associated with both obesity and substance abuse (1) implies that individual difference factors, such as affect regulation expectancies, modeling of overeating versus substance abuse, or environmental exposure (to high-fat foods versus psychoactive substances), interact with these general vulnerability factors to determine whether an at-risk individual develops obesity, substance abuse, or neither adverse outcome.

In conclusion, the present results strongly suggest that individuals who show blunted striatal activation during food intake are at

risk for obesity, particularly those at genetic risk for compromised dopamine signaling in brain regions implicated in food reward. Thus, behavioral or pharmacologic interventions that remedy striatal hypofunctioning may assist in the prevention and treatment of this pernicious health problem.

References and Notes

1. D. E. Comings, K. Blum, *Prog. Brain Res.* **126**, 325 (2000).
2. D. M. Small, M. Jones-Gotman, A. Dagher, *Neuroimage* **19**, 1709 (2003).
3. M. S. Szczypka et al., *Neuron* **30**, 819 (2001).
4. D. M. Small, R. J. Zatorre, A. Dagher, A. C. Evans, M. Jones-Gotman, *Brain* **124**, 1720 (2001).
5. G. Pagnoni, C. F. Zink, P. R. Montague, G. S. Berns, *Nat. Neurosci.* **5**, 97 (2002).
6. D. M. Small, M. G. Veldhuizen, J. Felsted, Y. E. Mak, F. McGlone, *Neuron* **57**, 786 (2008).
7. J. A. Gottfried, R. J. O'Doherty, R. J. Dolan, *Science* **301**, 1104 (2003).
8. J. de Leon et al., *J. Clin. Psychopharmacol.* **27**, 22 (2007).
9. J. J. Leddy et al., *Obes. Res.* **12**, 224 (2004).
10. G. J. Wang et al., *Lancet* **357**, 354 (2001).
11. N. D. Volkow et al., *Neuroimage* **42**, 1537 (2008).
12. S. O. Fetissov, M. M. Meguid, T. Sato, L. H. Zhang, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **283**, R905 (2002).
13. M. Orosco, C. Rouch, S. Nicolaidis, *Appetite* **26**, 1 (1996).
14. G. J. Wang, N. D. Volkow, J. S. Fowler, *Expert Opin. Ther. Targets* **6**, 601 (2002).
15. K. D'Ardenne, S. M. McClure, L. E. Nystrom, J. D. Cohen, *Science* **319**, 1264 (2008).
16. W. Schultz, P. Dayan, P. R. Montague, *Science* **275**, 1593 (1997).
17. B. Knutson, S. E. B. Gibbs, *Psychopharmacology (Berlin)* **191**, 813 (2007).
18. K. Blum et al., *Pharmacogenetics* **6**, 297 (1996).
19. M. R. Spitz et al., *Nutr. Res.* **20**, 371 (2000).
20. P. A. Tataranni et al., *Diabetes* **50**, 901 (2001).
21. E. P. Noble et al., *Arch. Gen. Psychiatry* **48**, 648 (1991).
22. J. Thompson et al., *Pharmacogenetics* **7**, 479 (1997).
23. T. Pohjalainen et al., *Mol. Psychiatry* **3**, 256 (1998).
24. E. G. Jonsson et al., *Mol. Psychiatry* **4**, 290 (1999).
25. T. Ritchie, E. P. Noble, *Neurochem. Res.* **28**, 73 (2003).
26. E. Tupala et al., *Neuroimage* **19**, 145 (2003).
27. M. Laruelle, J. Gelernter, R. Innis, *Mol. Psychiatry* **3**, 261 (1998).
28. E. P. Noble, *Am. J. Med. Genet.* **116B**, 103 (2003).
29. Materials and methods are available as supporting material on *Science* Online.
30. L. H. Epstein et al., *Behav. Neurosci.* **121**, 877 (2007).
31. N. D. Volkow, J. S. Fowler, G. J. Wang, *Behav. Pharmacol.* **13**, 355 (2002).
32. N. T. Bello, L. R. Lucas, A. Hajnal, *Neuroreport* **13**, 1575 (2002).
33. C. Colantuoni et al., *Neuroreport* **12**, 3549 (2001).
34. A. E. Kelley et al., *Eur. J. Neurosci.* **18**, 2592 (2003).