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What Twin Studies Tell Us about Brain Responses to Food Cues

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Abstract

Purpose of review—Functional magnetic resonance imaging (fMRI) using visual food cues provides insight into brain regulation of appetite in humans. This review sought evidence for genetic determinants of these responses.

Recent findings—Echoing behavioral studies of food cue responsiveness, twin study approaches detect significant inherited influences on brain response to food cues. Both polygenic (whole genome) factors and polymorphisms in single genes appear to impact appetite regulation, particularly in brain regions related to satiety perception. Furthermore, genetic confounding might underlie findings linking obesity to stereotypical response patterns on fMRI, i.e., associations with obesity may actually reflect underlying inherited susceptibilities rather than acquired levels of adiposity.

Summary—Insights from twin studies show that genes powerfully influence brain regulation of appetite, emphasizing the role of inherited susceptibility factors in obesity risk. Future research to delineate mechanisms of inherited obesity risk could lead to novel or more targeted interventional approaches.

Keywords

twin studies; fMRI; appetite regulation; obesity; genetics; food cues

Introduction

The rapid increase in prevalence of obesity in the U.S. over a relatively short period of 30–40 years has led to the supposition that today's obesity epidemic is almost entirely an environmental phenomenon, because genes at the population level do not change that

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Compliance with Ethics Guidelines

Conflict of Interest

Ellen Schur and Susan Carnell declare they have no conflict of interest.

Human and Animal Rights and Informed Consent

All reported studies/experiments with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

rapidly. However, classical twin studies consistently indicate that ~40–80% of the variance in BMI is due to inherited factors [1]. This apparently contradictory evidence can be reconciled by recognizing that every individual inherits a blend of protective and risk alleles of genes involved in energy homeostasis, the complex interactions among which convey relative risk of weight gain in an environment of nutritional abundance [2]. Inheritance across the whole genome, called “polygenic inheritance,” can be assessed in twin studies. Polygenic inheritance influences all aspects of energy homeostasis, including regulatory and hedonic aspects of ingestive behaviors [**3–7], whereas allelic variation in single genes has more specific effects [8]. Twin study approaches therefore have the potential to be informative about both inheritance of appetitive behaviors and the genetic factors that may put certain people at risk for obesity in the current food environment.

Use of fMRI to understand brain regulation of appetite

FMRI studies using visual food cues have emerged as a useful tool for elucidating brain regulation of appetite *in vivo* in humans. FMRI indirectly measures neural activity in response to a stimulus. Visual food cues are the most frequently utilized stimulus because of accumulated evidence showing that central nervous system (CNS) responses to images of food are regulated to control appetite and, perhaps, food intake as well. Visual images of food, particularly highly energetic foods, powerfully stimulate specific brain areas active in regulating energy homeostasis and reward processing [9–15]. Regional neural responses to visual food cues are suppressed by food ingestion [16, 17] and increase during fasting [15]. Moreover, specific CNS responses are reduced by anorexigenic appetite-regulating hormones [18–22] and enhanced by ghrelin, an orexigenic hormone [23]. The overall state of energy balance also modifies regional responses to visual food cues [12, 24]. Further, the strength of the effect of food ingestion on regional brain responses to high-calorie visual food cues provides a surrogate neurobiological measure of satiety in humans [16]. Accordingly, investigators have applied fMRI using visual food cues to better understand the neural basis of obesity. Studies [25, 13, 26, 17, 27] have suggested that obese persons show alterations in these responses, including evidence for increased activation of brain reward areas, altered activation of circuits involved in self-regulation, and differential responses to satiety, which could combine to promote overeating [28]. Recently, investigators have begun parsing the relative genetic and environmental influences on these responses using twin study approaches, the design of which vary according to the study purpose (Table 1). These studies have important implications for understanding the inherited basis of appetite regulation and obesity in humans.

Evidence from behavioral studies that food cue responsiveness is an inherited trait

Twin studies

The motivation for using twin studies to examine genetic influences on neural responses to food cues rests crucially on the existence of behavioral evidence for inherited influences on food cue responsiveness, i.e. the extent to which external food cues trigger a person to eat. External cue responsiveness was first implicated in obesity in classic studies by Schacter

[31]. More recently, genetic influences on this appetitive characteristic have been assessed within classical twin studies of children and infants using parent-report measures such as the Children's Eating Behavior Questionnaire (CEBQ) [32, 33] and Baby Eating Behavior Questionnaire (BEBQ) [34], and in studies of adults using self-report measures such as the Dutch Eating Behavior Questionnaire (DEBQ) [35], and Three Factor Eating Questionnaire (TFEQ) [36]. Typically, for the ***classical twin study*** approach, intraclass correlations within twin pairs for each sex and zygosity group are used to compare within-pair resemblance on the characteristic of interest among monozygotic (MZ) twins (who are genetically identical), and dizygotic (DZ) twins (who share half of their segregating genes). If MZ twins are more similar than DZ twins, genetic influence is inferred, with the difference in the degree of resemblance providing an indication of the heritability of the specified characteristic. Structural equation modeling can then use covariance between twins to test the fit of alternative genetic models and generate estimates of genetic effects.

Using such an approach, a UK study of 5435 MZ and DZ pairs of 8–11-year-old twins gave heritability estimates of 75% for scores on the CEBQ-Enjoyment of Food sub-scale, with shared environmental influences accounting for only 10% of correlations within twins [4]. Another parent-report questionnaire study of 147 MZ and 199 DZ twins from Quebec revealed that parents' responses about their child "eating too much" showed 87% heritability when assessed at 2.5 years of age (as well as a nonsignificant effect at 9 years of age) while "eating between meals" showed 24% heritability at 2.5 years of age and 81% at 9 years of age [37]. A UK study of 729 MZ and 1605 DZ infant twins revealed heritability of 59% for scores on the BEBQ-Food Responsiveness sub-scale and 53% for scores on BEBQ-Enjoyment of Food [38].

Similar results have been obtained in adults. For example, a Korean study including 443 MZ twin pairs and 124 same-sex DZ twin pairs obtained heritability estimates of 21% for scores on the DEBQ-External Eating sub-scale [39]. A study of 129 MZ pairs and 81 DZ pairs of female twins estimated heritability of scores on the TFEQ-Disinhibition sub-scale at 45% [40], while a study of 456 MZ and 326 DZ pairs of male twins used a modified TFEQ to reveal 45% heritability of a scale measuring uncontrolled eating [41], and a study using samples of 314 MZ and 327 DZ same-sex British and Finnish twins found that genetic influences accounted for 45–69% of variation in uncontrolled eating [42]. While heritability estimates vary substantially depending on measures, methods and populations, these results agree in implicating a significant degree of heritability for food cue responsiveness in both children and adults.

Familial risk

Convergent evidence for the heritability of food cue responsiveness also comes from studies reporting relationships between parent weight (which is associated with offspring weight in childhood and throughout development [43–49]), and food cue responsiveness in offspring. For example, measuring intake of palatable energy-dense snack foods at an Eating in the Absence of Hunger (EAH) test [50, 51] in 5-year-old children at high- vs. low- familial obesity risk based on maternal pre-pregnancy weight, revealed that high-risk boys consumed more than twice the calories consumed by low-risk boys [52]. In another study, EAH intake

was assessed in 197 girls at 5, 7, 9, 11, and 13 years of age [53]. Girls with two overweight parents ate significantly more during the EAH test and showed significantly larger increases in disinhibited eating over time compared to counterparts with none or only one parent overweight.

Some evidence also supports correlations in food cue responsiveness between parents and offspring. For example, in studies using the TFEQ, mothers' scores on uncontrolled eating have been associated with those of their daughters in two separate samples (r=0.22 [54]; r=0.17 [55]), while another study observed mother-daughter correlations for scores on TFEQ-Disinhibition (r=0.24), and TFEQ-Hunger (r=0.31) [56]. A study using the DEBQ found that parents' External Eating scores correlated with those scores in their 12 year old children [57].

Other studies have used designs including multiple family members to generate heritability estimates. For example, in a study of 725 4–19-year old children from 300 Hispanic families that estimated heritability based on similarities and differences between siblings rather than twins, intake of palatable energy-dense snack foods at an EAH test [50, 58] was revealed to be 51% heritable [59]. Using questionnaire measures, a family study of 624 Old Order Amish adults from 28 families obtained a heritability estimate of 40% for TFEQ-Disinhibition [60].

Single nucleotide polymorphisms

Since genome-wide association approaches revealed single nucleotide polymorphisms on the fat mass and obesity-associated gene (*FTO)* to be the first common genetic variants to be associated with obesity at a population level [61], a number of behavioral studies have converged to suggest that this variation may act in part by enhancing food cue responsiveness. For example, in a UK study of 131 4–5 year olds in which EAH intake was assessed at the participants' homes using a free-access procedure that provided three varieties of (sweet and savory) biscuit snacks to children, those with one or two copies of the A (risk) allele for the *FTO* polymorphism rs9939609 consumed significantly more biscuits in the absence of hunger compared to children with no risk allele [62]. Supporting this result, other studies have demonstrated high-risk alleles on *FTO* to be associated with increased energy intake [63–66], increased intake of dietary fat [67, 68] and protein [69], and perceived loss of control over eating [70].

Evidence that response to visual food cues is an inherited trait

Twin studies

Recent neuroimaging research suggests that brain response to visual food cues has inherited influences. A study by Melhorn et al. [**3] enrolled 21 MZ twin pairs from a community-based registry in Washington State [71]. This experimental MZ design echoed formative twin studies conducted by Bouchard and colleagues showing that the amount of weight gained during 100 days of overfeeding has an inherited basis [2] as does the response to negative energy balance [72]. MZ twins are genetically identical, of the exact same age and sex, and also matched for numerous unmeasured and familial environmental factors. The

experimental MZ twin study design used by both the Bouchard et al. and Melhorn et al. studies exerts an environmental stimulus on all subjects and then compares the within-pair to between-pair variance in response to the stimulus by testing for a significant intraclass correlation. If the between-pair variance is larger, then twins are presumed to respond more similarly because of inherited and familial factors [29, 73]. In Melhorn et al., twin pairs underwent an fMRI using a visual food cue paradigm that compares activation by images of "fattening" food, "nonfattening" food, and non-food objects. Foods in the fattening group were uniformly high in energy content and were previously rated as food that should be avoided when trying to lose weight (e.g., pizza, desserts, French fries) [74]. Nonfattening food images depicted low-calorie and low energy density foods (e.g., fruits, vegetables, lean meats). Non-food object images depict easily recognizable discrete items (e.g., electronics, pencils, furniture). The strength of activation by fattening food cues within specific brain regions regulating appetite and reward perception has previously been shown to be a marker of subjective satiety [16]. The identified regions participate in an extended satiety network that includes the amygdala, ventral striatum, insula, dorsal striatum, ventral tegmental area/ substantia nigra and medial orbitofrontal cortex (mOFC). Twins underwent the fMRI paradigm before and after eating a standardized meal that was titrated to 20% of each individual's estimated daily caloric needs. Before the meal, there was no evidence for inherited influences on responsivity to fattening food cues (vs. nonfattening) in a region of interest (ROI) analysis. However, after the standardized meal, twins' mean level of activation by fattening food cues across an extended satiety network was significantly more similar than that of the unrelated individuals in the study. Moreover, Melhorn et al. also found evidence for inherited influences on the extent that activation was changed by consuming the meal. Individual ROIs in which evidence for inherited influence on meal-induced satiety was strongest were the amygdala, dorsal striatum, mOFC, and the ventral tegmental area. Because MZ twins share 100% of their genes, these data provide robust support for the conclusion that the degree of satiety induced by a meal is an inherited influence on appetite regulation with potential implications for heritability of obesity.

Additional evidence comes from a recent ***co-twin control study*** by Doornweerd et al. [**75]. They studied a sample of Dutch twins who were selected to be discordant for BMI. A discordant MZ twin study is useful for understanding to what extent a phenotype, in this case adiposity, is related to the outcome of interest, independent of genetics. This interpretation is feasible because twins are compared to each other, hence, sex, age, familial, and genomic factors are controlled by the twin design. Doornweerd et al. enrolled 16 BMI-discordant MZ pairs who were, on average, in the overweight range. They utilized 2 paradigms: one measured brain activation by high- and low-calorie food images and a second measured activation during anticipation and receipt of a small volume of chocolate milkshake onto the tongue. Their analyses focused on ROIs in the amygdala, insula, caudate nucleus, putamen, and OFC. As compared to the leaner members of the pairs, they found no brain regions in which heavier twins had significantly different brain activation by either visual food cues or anticipation and receipt of the milkshake. The study has two important implications. First, it provides strong evidence that genetic pleiotropy (referring, in this case, to the phenomenon that single genes can influence more than one trait [76]) may underlie prior findings associating obesity with brain response to food cues. In other words, genetic

confounding exists such that findings relating activation to obesity could be due to genetic influences on both traits rather than adiposity itself. Second, it supports the overall inherited influence on brain response to food cues because controlling for genetics minimized responses seen in the overall group.

Familial risk

A small number of studies have used a familial risk design to investigate the heritability of neural responses to food cues. In the first study to use this approach, 35 lean adolescents with two obese or overweight parents (high familial risk group) and 25 lean adolescents with two lean parents (low familial risk group) underwent fMRI scanning while exposed to small tastes of milkshake (consummatory reward), and cues indicating imminent administration of the milkshake taste (anticipated reward). Greater caudate, frontal operculum and parietal operculum responses to milkshake tastes were observed in the high-risk group, consistent with greater engagement of circuitry involved in taste reward during food consumption. However, there were no group differences in response to a simple cue indicating imminent administration of a milkshake taste (i.e., anticipated food reward) [77]. In a more recent study, 10 overweight/obese adolescents, 16 lean adolescents with obese/overweight biological mothers (high familial risk group) and 10 lean adolescents with lean biological mothers (low familial risk group) underwent fMRI scanning while viewing words denoting a variety of commonly consumed high-calorie foods, low-calorie foods, and non-foods, and providing ratings indicating how much they wanted to consume each of the foods [78]. Adolescents at high familial risk exhibited weaker activation of an attentional/regulatory system including dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, and basal ganglia nuclei, with activation being greatest in the lean/low familial risk group, intermediate in the lean/high familial risk group, and weakest in the overweight/obese group. These group differences were most apparent for neural responses to high- compared with low-calorie food words. Although this design does not allow genetic and environmental elements of familial risk to be distinguished, these results are consistent with an inherited component to activation of self-regulatory circuits in the brain when exposed to cues recalling a variety of commonly-consumed foods, particularly high-calorie foods, within an evaluative context.

Single nucleotide polymorphisms

Single-gene studies have detected that allelic variation at loci linked to obesity or appetite regulation also influences visual response to food cues. Though rare, forms of monogenic obesity exert profound influences, usually in early childhood, on appetite and body weight. CNS effects of these single gene mutations suggest that hunger and motivation for food is enhanced via genetic leptin deficiency [19, 18] whereas responses in regions associated with behavioral inhibition are diminished [18]. In 8 obese individuals with melanocortin-4 receptor (MC4R) mutations, brain response to food cues in striatal regions was elevated compared to 10 subjects with obesity unrelated to MC4R. In contrast to monogenic obesity, allelic variation in *FTO* is associated with obesity risk at a population level [79]. FMRI studies of subjects with high-risk genotypes for *FTO* have shown greater responsivity to food commercials in the ventral striatum (nucleus accumbens) in children [*80] and food images in the putamen in adults [81]. Both could indicate heightened reward sensitivity or

motivation for food intake, whereas findings of greater activation by food cues in the posterior fusiform gyrus in a ROI analysis suggest enhanced visual attention for food [82]. In contrast, reduced inhibitory control is supported by findings that at-risk genotype carriers show less prefrontal cortical activation by food cues after a glucose load [83]. Other studies suggest that reward learning may be altered, particularly when genetic polymorphisms that reduce dopamine signaling capacity co-occur [84]. Taken together, these findings suggest greater responsivity to highly energetic foods in appetitive regions among people with high-risk *FTO* genotypes, particularly in a satiated state and subjects with higher BMIs [81]. Finally, much attention has focused on genetic variants associated with reduced striatal dopamine receptor density (TaqIA A1 allele). Studies utilizing anticipation and receipt of palatable taste cues suggest effect modification by the presence of the risk alleles. Individuals carrying risk alleles are at risk of weight gain related to hypo-responsivity to food cues or taste receipt within dorsal striatal regions (caudate) [85, 86], whereas in non-carriers, hyper-responsivity promotes obesity risk. While the interpretation of such findings as a deficit in experienced reward has been debated [87, 88], inherited variability in dopamine-dependent neural signaling clearly influences components of CNS appetite regulation and obesity risk directly [89, 8, 90] and via interactions with other risk genes [84, 91].

The discrepant findings based on single-gene analyses are perhaps indicative of the relatively small influence of a single gene on the phenotype of body weight as well as the divergent CNS pathways whereby a single gene might influence obesity pathogenesis. Moreover, each individual inherits a blend of risk and protective alleles, which could also increase variability within samples enrolled in single-gene association studies. Moreover, these studies might also be misleading when genetic effects are modified by other inherited factors [84, 91], sex, BMI [82, 81], or the particular loci under investigation [92]. Finally, normal weight adults with high-risk genotypes may have neural responsiveness that differs from high-risk allele carriers who are vulnerable to weight gain, and some results are derived from exclusively normal weight samples [93, 82, 84]. For example, one study comparing 10 normal weight high-risk AA genotype (*FTO* rs 9939609) men to 10 normal weight TT low-risk men, found less responsivity to food cues in regions including the thalamus, hypothalamus, ventral tegmental area/substantia nigra, insula, globus pallidus, and hippocampus [93]. In contrast to single-gene studies, observed effects related to genetics in twin studies are attributable to the whole genome and thus inherited influences on numerous CNS pathways as well as both risk and protective factors are simultaneously investigated. These differences in approach may explain why twin studies to date show robust overall inherited influences on brain regulation of appetite whereas findings related to single genes remain incongruent. In sum, accumulated evidence from a variety of approaches strongly suggests that brain response to food cues has inherited influences, reflecting genetically driven variation in CNS appetite regulation.

Evidence that brain regulation of appetite has environmental influences that are independent of genetics

Co-twin control studies have the unique ability to discern whether environmental influences on a trait are independent of genetics. Apart from a randomized, controlled trial, a discordant MZ twin study is the most rigorous means of approaching causal inference through an observational study [94]. The Doornweerd et al. study discussed above is an example of a study that utilized this design to refute independent environmental effects of adiposity on response to visual food cues [**75]. Instead, their negative result emphasizes the importance of inherited factors on brain regulation of appetite. The same group, however, found evidence for difference in functional connectivity between heavier and leaner twins (N= 16 pairs). Using resting state fMRI, in which neural activity is measured in the absence of any stimulus, they showed reduced connectivity of the bilateral putamen within a basal ganglia network [*95] in heavier compared to leaner MZ twins. The finding indicates that, at higher levels of adiposity, the putamen is relatively disengaged from a network of distributed brain regions governing motor as well as associative tasks [96], regardless of genetic background. In a ***co-twin control study*** of 10 MZ twin pairs, Schur et al. found greater activation among restrained eaters by high-calorie, “fattening” food cues before eating in the left amygdala, thalamus, and occipital cortex as compared to their unrestrained eating co-twins [97]. Restrained eaters also showed significantly greater decreases in activation by fattening food cues from before to after a milkshake in the amygdala and occipital cortex. In contrast, restrained eating twins, demonstrated significantly increased activation by non-fattening food cues after drinking a milkshake in the mOFC and occipital lobe. These findings demonstrate that adopting a long-term behavioral pattern of intentional weight control is an environmental influence that can result in acquired differences in CNS regulation of appetite.

Limitations of the current literature and future directions

While the current literature has utilized a variety of twin approaches to discern inherited influences on brain response to food cues, a classical twin study is the only design that can parse the relative genetic and environmental contributions. In the absence of such a study, the heritability of the trait of brain response to visual food cues remains unknown. Twin studies are inherently controlled for confounding by sex. This does not, however, rule out effect modification, and no studies to date have had large enough samples of male and female twin pairs to effectively test for variation in genetic influence on neural responsiveness by sex. In addition, much of the literature has used ROI approaches, and whole brain analyses could reveal additional regions under genetic control that have not been previously examined. Finally, although hypothesized to be driving food intake, there is little evidence connecting altered brain activation by visual food cues in obesity to *ad libitum* food consumption. One study has positively associated responses to high-calorie food cues in the mOFC, amygdala, insula and ventral striatum to the percentage of fat consumed at an *ad libitum* buffet meal [16]. A second study has correlated total calories consumed at a buffet meal with differences between brain response to food images in insula, caudate and OFC during glucagon-like peptide-1 agonist vs. saline infusion [22]. Additional data are

needed to discern the specific regions and pathways in which fMRI-assessed responses to food cues are most closely linked to food choice, macronutrient regulation, or caloric consumption. Finally, research into molecular mechanisms by which allelic variation conveys higher obesity risk is ongoing [93, 98], but recent rodent data show that impaired leptin signaling in neurons could link polymorphisms in *FTO* to hyperphagia and weight gain [*99, 98].

Conclusions

Echoing behavioral studies of food cue responsiveness, twin study approaches that assess the overall effect of the whole genome provide important evidence that brain regulation of appetite has inherited influences. To date, study results for polymorphisms in single genes have yet to coalesce around specific pathways or affected regions. Studies that use a whole-brain analytic approach, include both lean and obese carriers of risk alleles, and carefully control for satiety state could yield more consistent findings. Furthermore, the high heritability of obesity and potential that this inheritance is reflected at the level of the brain makes it important to consider genetic confounding in studies of obesity. Caution is warranted in interpretations that obesity or excess adiposity is an acquired trait with characteristic response patterns on fMRI. Such conclusions likely underestimate the influences of both inherited susceptibilities and potential behavioral or environmental factors that are important determinants of brain response to food cues. Future research to delineate molecular mechanisms of inherited obesity risk could lead to novel interventional approaches. In the meantime, research on the utility of translating findings of genetic susceptibility into targeted preventative and interventional strategies is needed to advance the field.

References

Papers of particular relevance, published recently, have been denoted as:

* Of importance or ** Of outstanding importance

1. Yang W, Kelly T, He J. Genetic epidemiology of obesity. Epidemiol Rev. 2007; 29:49–61. DOI: 10.1093/epirev/mxm004 [PubMed: 17566051]
2. Bouchard C, Tremblay A, Despres JP, Nadeau A, Lupien PJ, Theriault G, et al. The response to long-term overfeeding in identical twins. N Engl J Med. 1990; 322(21):1477–82. [PubMed: 2336074]
**3. Melhorn SJ, Mehta S, Kratz M, Tyagi V, Webb MF, Noonan CJ, et al. Brain regulation of appetite in twins. Am J Clin Nutr. 2016; 103(2):314–22. Demonstrates inherited influence on brain response to high-calorie food cues after eating as well as meal-induced reductions in brain response to high-calorie food cues. DOI: 10.3945/ajcn.115.121095 [PubMed: 26739033]
4. Carnell S, Haworth CM, Plomin R, Wardle J. Genetic influence on appetite in children. Int J Obes. 2008; 32(10):1468–73.
5. Schur E, Noonan C, Polivy J, Goldberg J, Buchwald D. Genetic and environmental influences on restrained eating behavior. Int J Eat Disord. 2009; 42(8):765–72. [PubMed: 19658171]
6. de Castro JM, Lilenfeld LR. Influence of heredity on dietary restraint, disinhibition, and perceived hunger in humans. Nutrition. 2005; 21(4):446–55. [PubMed: 15811764]
7. de Castro JM. Heredity influences the dietary energy density of free-living humans. Physiol Behav. 2006; 87(1):192–8. [PubMed: 16310814]

8. Stice E, Spoor S, Bohon C, Small DM. Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. Science. 2008; 322(5900):449–52. [PubMed: 18927395]
9. Schur EA, Kleinhans NM, Goldberg J, Buchwald D, Schwartz MW, Maravilla K. Activation in brain energy regulation and reward centers by food cues varies with choice of visual stimulus. Int J Obes Relat Metab Disord. 2009; 33(6):653–61.
10. Uher R, Treasure J, Heining M, Brammer MJ, Campbell IC. Cerebral processing of food-related stimuli: effects of fasting and gender. Behav Brain Res. 2006; 169(1):111–9. [PubMed: 16445991]
11. Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Cortical and limbic activation during viewing of high- versus low-calorie foods. Neuroimage. 2003; 19(4): 1381–94. [PubMed: 12948696]
12. Cornier MA, Von Kaenel SS, Bessesen DH, Tregellas JR. Effects of overfeeding on the neuronal response to visual food cues. Am J Clin Nutr. 2007; 86(4):965–71. [PubMed: 17921372]
13. Rothemund Y, Preuschhof C, Bohner G, Bauknecht HC, Klingebiel R, Flor H, et al. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. Neuroimage. 2007; 37(2):410–21. [PubMed: 17566768]
14. Toepel U, Knebel JF, Hudry J, le Coutre J, Murray MM. The brain tracks the energetic value in food images. Neuroimage. 2009; 44(3):967–74. [PubMed: 19013251]
15. Goldstone AP, de Hernandez CGP, Beaver JD, Muhammed K, Croese C, Bell G, et al. Fasting biases brain reward systems towards high-calorie foods. Eur J Neurosci. 2009; 30(8):1625–35. [PubMed: 19811532]
16. Mehta S, Melhorn SJ, Smeraglio A, Tyagi V, Grabowski T, Schwartz MW, et al. Regional brain response to visual food cues is a marker of satiety that predicts food choice. Am J Clin Nutr. 2012; 96(5):989–99. DOI: 10.3945/ajcn.112.042341 [PubMed: 22990034]
17. Bruce AS, Holsen LM, Chambers RJ, Martin LE, Brooks WM, Zarcone JR, et al. Obese children show hyperactivation to food pictures in brain networks linked to motivation, reward and cognitive control. Int J Obes. 2010; 34(10):1494–500. DOI: 10.1038/ijo.2010.84
18. Baicy K, London ED, Monterosso J, Wong ML, Delibasi T, Sharma A, et al. Leptin replacement alters brain response to food cues in genetically leptin-deficient adults. Proc Natl Acad Sci U S A. 2007; 104(46):18276–9. [PubMed: 17986612]
19. Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. Leptin regulates striatal regions and human eating behavior. Science. 2007; 317(5843):1355. [PubMed: 17690262]
20. De Silva A, Salem V, Long CJ, Makwana A, Newbould RD, Rabiner EA, et al. The gut hormones PYY 3-36 and GLP-1 7-36 amide reduce food intake and modulate brain activity in appetite centers in humans. Cell Metab. 2011; 14(5):700–6. DOI: 10.1016/j.cmet.2011.09.010 [PubMed: 22000927]
21. Guthoff M, Grichisch Y, Canova C, Tschritter O, Veit R, Hallschmid M, et al. Insulin modulates food-related activity in the central nervous system. J Clin Endocrinol Metab. 2010; 95(2):748–55. [PubMed: 19996309]
22. van Bloemendaal L, RG IJ, Ten Kulve JS, Barkhof F, Konrad RJ, Drent ML, et al. GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. Diabetes. 2014; 63(12): 4186–96. DOI: 10.2337/db14-0849 [PubMed: 25071023]
23. Malik S, McGlone F, Bedrossian D, Dagher A. Ghrelin modulates brain activity in areas that control appetitive behavior. Cell Metab. 2008; 7(5):400–9. [PubMed: 18460331]
24. Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. J Clin Invest. 2008; 118(7): 2583–91. [PubMed: 18568078]
25. Stoeckel LE, Weller RE, Cook EW, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage. 2008; 41(2): 636–47. [PubMed: 18413289]
26. Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. J Abnorm Psychol. 2008; 117(4):924–35. [PubMed: 19025237]

27. Dimitropoulos A, Tkach J, Ho A, Kennedy J. Greater corticolimbic activation to high-calorie food cues after eating in obese vs. normal-weight adults. Appetite. 2012; 58(1):303–12. DOI: 10.1016/j.appet.2011.10.014 [PubMed: 22063094]
28. Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: current knowledge and future directions. Obes Rev. 2012; 13(1):43–56. DOI: 10.1111/j.1467-789X.2011.00927.x [PubMed: 21902800]
29. Bouchard C, Tremblay A. Genetic influences on the response of body fat and fat distribution to positive and negative energy balances in human identical twins. J Nutr. 1997; 127(5 Suppl):943S–7S. [PubMed: 9164270]
30. Carlin JB, Gurrin LC, Sterne JA, Morley R, Dwyer T. Regression models for twin studies: a critical review. Int J Epidemiol. 2005; 34(5):1089–99. [PubMed: 16087687]
31. Schachter S. Obesity and eating. Internal and external cues differentially affect the eating behavior of obese and normal subjects. Science. 1968; 161(843):751–6. [PubMed: 5663800]
32. Wardle J, Guthrie CA, Sanderson S, Rapoport L. Development of the Children's Eating Behaviour Questionnaire. J Child Psychol Psychiatry. 2001; 42(7):963–70. [PubMed: 11693591]
33. Carnell S, Wardle J. Measuring behavioural susceptibility to obesity: validation of the child eating behaviour questionnaire. Appetite. 2007; 48(1):104–13. DOI: 10.1016/j.appet.2006.07.075 [PubMed: 16962207]
34. Llewellyn CH, van Jaarsveld CH, Johnson L, Carnell S, Wardle J. Development and factor structure of the Baby Eating Behaviour Questionnaire in the Gemini birth cohort. Appetite. 2011; 57(2):388–96. DOI: 10.1016/j.appet.2011.05.324 [PubMed: 21672566]
35. Van Strien T, Frijters JE, Bergers GP, Defares PB. The Dutch Eating Behavior Questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior. Int J Eat Disor. 1986; 5:295–315.
36. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res. 1985; 29(1):71–83. [PubMed: 3981480]
37. Dubois L, Diasparra M, Bedard B, Kaprio J, Fontaine-Bisson B, Tremblay R, et al. Genetic and environmental influences on eating behaviors in 2.5- and 9-year-old children: a longitudinal twin study. Int J Behav Nutr Phys Act. 2013; 10:134.doi: 10.1186/1479-5868-10-134 [PubMed: 24313977]
38. Llewellyn CH, van Jaarsveld CH, Johnson L, Carnell S, Wardle J. Nature and nurture in infant appetite: analysis of the Gemini twin birth cohort. Am J Clin Nutr. 2010; 91(5):1172–9. DOI: 10.3945/ajcn.2009.28868 [PubMed: 20335548]
39. Sung J, Lee K, Song YM, Lee MK, Lee DH. Heritability of eating behavior assessed using the DEBQ (Dutch Eating Behavior Questionnaire) and weight-related traits: the Healthy Twin Study. Obesity. 2010; 18(5):1000–5. DOI: 10.1038/oby.2009.389 [PubMed: 19876000]
40. Neale BM, Mazzeo SE, Bulik CM. A twin study of dietary restraint, disinhibition and hunger: an examination of the eating inventory (three factor eating questionnaire). Twin Res. 2003; 6(6):471–8. [PubMed: 14965456]
41. Tholin S, Rasmussen F, Tynelius P, Karlsson J. Genetic and environmental influences on eating behavior: the Swedish Young Male Twins Study. Am J Clin Nutr. 2005; 81(3):564–9. [PubMed: 15755823]
42. Keskitalo K, Tuorila H, Spector TD, Cherkas LF, Knaapila A, Kaprio J, et al. The Three-Factor Eating Questionnaire, body mass index, and responses to sweet and salty fatty foods: a twin study of genetic and environmental associations. Am J Clin Nutr. 2008; 88(2):263–71. [PubMed: 18689360]
43. Epstein LH, Temple JL, Neaderhiser BJ, Salis RJ, Erbe RW, Leddy JJ. Food reinforcement, the dopamine D2 receptor genotype, and energy intake in obese and nonobese humans. Behav Neurosci. 2007; 121(5):877–86. DOI: 10.1037/0735-7044.121.5.877 [PubMed: 17907820]
44. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med. 1997; 337(13):869–73. DOI: 10.1056/NEJM199709253371301 [PubMed: 9302300]

45. Crossman A, Anne Sullivan D, Benin M. The family environment and American adolescents' risk of obesity as young adults. Soc Sci Med. 2006; 63(9):2255–67. DOI: 10.1016/j.socscimed.2006.05.027 [PubMed: 16828216]
46. Whitaker KL, Jarvis MJ, Beeken RJ, Boniface D, Wardle J. Comparing maternal and paternal intergenerational transmission of obesity risk in a large population-based sample. Am J Clin Nutr. 2010; 91(6):1560–7. DOI: 10.3945/ajcn.2009.28838 [PubMed: 20375189]
47. Burke V, Beilin LJ, Dunbar D. Family lifestyle and parental body mass index as predictors of body mass index in Australian children: a longitudinal study. Int J Obes Relat Metab Disord. 2001; 25(2):147–57. DOI: 10.1038/sj.ijo.0801538 [PubMed: 11410813]
48. Magarey AM, Daniels LA, Boulton TJ, Cockington RA. Predicting obesity in early adulthood from childhood and parental obesity. Int J Obes Relat Metab Disord. 2003; 27(4):505–13. DOI: 10.1038/sj.ijo.0802251 [PubMed: 12664084]
49. Epstein LH, Yokum S, Feda DM, Stice E. Food reinforcement and parental obesity predict future weight gain in non-obese adolescents. Appetite. 2014; 82:138–42. DOI: 10.1016/j.appet.2014.07.018 [PubMed: 25045864]
50. Fisher JO, Birch LL. Restricting access to foods and children's eating. Appetite. 1999; 32(3):405–19. DOI: 10.1006/appe.1999.0231 [PubMed: 10336797]
51. Fisher JO, Birch LL. Eating in the absence of hunger and overweight in girls from 5 to 7 y of age. Am J Clin Nutr. 2002; 76(1):226–31. [PubMed: 12081839]
52. Faith MS, Berkowitz RI, Stallings VA, Kerns J, Storey M, Stunkard AJ. Eating in the absence of hunger: a genetic marker for childhood obesity in prepubertal boys? Obesity. 2006; 14(1):131–8. DOI: 10.1038/oby.2006.16 [PubMed: 16493131]
53. Francis LA, Ventura AK, Marini M, Birch LL. Parent overweight predicts daughters' increase in BMI and disinhibited overeating from 5 to 13 years. Obesity. 2007; 15(6):1544–53. DOI: 10.1038/oby.2007.183 [PubMed: 17557992]
54. de Lauzon-Guillain B, Romon M, Musher-Eizenman D, Heude B, Basdevant A, Charles MA. Cognitive restraint, uncontrolled eating and emotional eating: correlations between parent and adolescent. Matern Child Nutr. 2009; 5(2):171–8. DOI: 10.1111/j.1740-8709.2008.00164.x [PubMed: 19292751]
55. Elfhag K, Linne Y. Gender differences in associations of eating pathology between mothers and their adolescent offspring. Obes Res. 2005; 13(6):1070–6. DOI: 10.1038/oby.2005.125 [PubMed: 15976150]
56. Provencher V, Perusse L, Bouchard L, Drapeau V, Bouchard C, Rice T, et al. Familial resemblance in eating behaviors in men and women from the Quebec Family Study. Obes Res. 2005; 13(9):1624–9. [PubMed: 16222066]
57. Elfhag K, Tynelius P, Rasmussen F. Family links of eating behaviour in normal weight and overweight children. Int J Pediatr Obes. 2010; 5(6):491–500. DOI: 10.3109/17477160903497001 [PubMed: 20233161]
58. Fisher JO, Birch LL. Eating in the absence of hunger and overweight in girls from 5 to 7 y of age. Am J Clin Nutr. 2002; 76(1):226–31. [PubMed: 12081839]
59. Fisher JO, Cai G, Jaramillo SJ, Cole SA, Comuzzie AG, Butte NF. Heritability of hyperphagic eating behavior and appetite-related hormones among Hispanic children. Obesity. 2007; 15(6):1484–95. DOI: 10.1038/oby.2007.177 [PubMed: 17557986]
60. Steinle NI, Hsueh WC, Snitker S, Pollin TI, Sakul H, St Jean PL, et al. Eating behavior in the Old Order Amish: heritability analysis and a genome-wide linkage analysis. Am J Clin Nutr. 2002; 75(6):1098–106. [PubMed: 12036819]
61. Loos RJ, Yeo GS. The bigger picture of FTO: the first GWAS-identified obesity gene. Nat Rev Endocrinol. 2014; 10(1):51–61. DOI: 10.1038/nrendo.2013.227 [PubMed: 24247219]
62. Wardle J, Llewellyn C, Sanderson S, Plomin R. The FTO gene and measured food intake in children. Int J Obes. 2009; 33(1):42–5.
63. Cecil JE, Tavendale R, Watt P, Hetherington MM, Palmer CN. An obesity-associated FTO gene variant and increased energy intake in children. N Engl J Med. 2008; 359(24):2558–66. [PubMed: 19073975]

64. Speakman JR, Rance KA, Johnstone AM. Polymorphisms of the FTO gene are associated with variation in energy intake, but not energy expenditure. Obesity (Silver Spring). 2008; 16(8):1961–5. [PubMed: 18551109]

65. Timpson NJ, Emmett PM, Frayling TM, Rogers I, Hattersley AT, McCarthy MI, et al. The fat mass- and obesity-associated locus and dietary intake in children. Am J Clin Nutr. 2008; 88(4): 971–8. [PubMed: 18842783]

66. Sonestedt E, Roos C, Gullberg B, Ericson U, Wirfalt E, Orho-Melander M. Fat and carbohydrate intake modify the association between genetic variation in the FTO genotype and obesity. Am J Clin Nutr. 2009; 90(5):1418–25. DOI: 10.3945/ajcn.2009.27958 [PubMed: 19726594]

67. Lee HJ, Kim IK, Kang JH, Ahn Y, Han BG, Lee JY, et al. Effects of common FTO gene variants associated with BMI on dietary intake and physical activity in Koreans. Clinica chimica acta. 2010; 411(21–22):1716–22. DOI: 10.1016/j.cca.2010.07.010

68. Park SL, Cheng I, Pendergrass SA, Kucharska-Newton AM, Lim U, Ambite JL, et al. Association of the FTO obesity risk variant rs8050136 with percentage of energy intake from fat in multiple racial/ethnic populations: the PAGE study. Am J Epidemiol. 2013; 178(5):780–90. DOI: 10.1093/aje/kwt028 [PubMed: 23820787]

69. Ahmad T, Lee IM, Pare G, Chasman DI, Rose L, Ridker PM, et al. Lifestyle interaction with fat mass and obesity-associated (FTO) genotype and risk of obesity in apparently healthy U.S. women. Diabetes Care. 2011; 34(3):675–80. DOI: 10.2337/dc10-0948 [PubMed: 21266646]

70. Tanofsky-Kraff M, Han JC, Anandalingam K, Shomaker LB, Columbo KM, Wolkoff LE, et al. The FTO gene rs9939609 obesity-risk allele and loss of control over eating. Am J Clin Nutr. 2009; 90(6):1483–8. DOI: 10.3945/ajcn.2009.28439 [PubMed: 19828706]

71. Strachan E, Hunt C, Afari N, Duncan G, Noonan C, Schur E, et al. University of Washington Twin Registry: poised for the next generation of twin research. Twin Res Hum Genet. 2013; 16(1):455–62. DOI: 10.1017/thg.2012.124 [PubMed: 23218177]

72. Bouchard C, Tremblay A, Despres JP, Theriault G, Nadeau A, Lupien PJ, et al. The response to exercise with constant energy intake in identical twins. Obes Res. 1994; 2(5):400–10. [PubMed: 16358397]

73. Bouchard C. Heredity and the path to overweight and obesity. Med Sci Sports Exerc. 1991; 23(3): 285–91. [PubMed: 2020265]

74. Schur EA, Kleinhans NM, Goldberg J, Buchwald D, Schwartz MW, Maravilla K. Activation in brain energy regulation and reward centers by food cues varies with choice of visual stimulus. Int J Obes. 2009; 33(6):653–61. DOI: 10.1038/ijo.2009.56

**75. Doornweerd S, De Geus EJ, Barkhof F, Van Bloemendaal L, Boomsma DI, Van Dongen J, et al. Brain reward responses to food stimuli among female monozygotic twins discordant for BMI. Brain Imaging Behav. 2017; Heavier twins did not have different responses to visual food cues in selected brain regions regulating appetite. The study suggests genetic confounding is present in studies showing altered brain response to visual food cues in obesity (i.e., that inherited factors rather than adiposity *per se* explain the findings). doi: 10.1007/s11682-017-9711-1

76. Paaby AB, Rockman MV. The many faces of pleiotropy. Trends Genet. 2013; 29(2):66–73. DOI: 10.1016/j.tig.2012.10.010 [PubMed: 23140989]

77. Stice E, Yokum S, Burger KS, Epstein LH, Small DM. Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. J Neurosci. 2011; 31(12):4360–6. DOI: 10.1523/JNEUROSCI.6604-10.2011 [PubMed: 21430137]

78. Carnell S, Benson L, Chang KV, Wang Z, Huo Y, Geliebter A, et al. Neural correlates of familial obesity risk and overweight in adolescence. Neuroimage. 2017; 159:236–47. DOI: 10.1016/j.neuroimage.2017.07.052 [PubMed: 28754348]

79. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet. 2009; 41(1):25–34. [PubMed: 19079261]

*80. Rapuano KM, Zieselman AL, Kelley WM, Sargent JD, Heatherton TF, Gilbert-Diamond D. Genetic risk for obesity predicts nucleus accumbens size and responsivity to real-world food cues. Proc Natl Acad Sci U S A. 2017; 114(1):160–5. Establishes that children with high risk genotypes at the rs9939609 locus in the fat mass and obesity-associated gene (*FTO*) have greater

nucleus accumbens size and responsivity to food commercials, indicating enhanced motivation and responsiveness to common environmental food stimuli. DOI: 10.1073/pnas.1605548113 [PubMed: 27994159]

81. Wiemerslage L, Nilsson EK, Solstrand Dahlberg L, Ence-Eriksson F, Castillo S, Larsen AL, et al. An obesity-associated risk allele within the FTO gene affects human brain activity for areas important for emotion, impulse control and reward in response to food images. Eur J Neurosci. 2016; 43(9):1173–80. DOI: 10.1111/ejn.13177 [PubMed: 26797854]
82. Kuhn AB, Feis DL, Schilbach L, Kracht L, Hess ME, Mauer J, et al. FTO gene variant modulates the neural correlates of visual food perception. Neuroimage. 2016; 128:21–31. DOI: 10.1016/j.neuroimage.2015.12.049 [PubMed: 26767945]
83. Heni M, Kullmann S, Veit R, Ketterer C, Frank S, Machicao F, et al. Variation in the obesity risk gene FTO determines the postprandial cerebral processing of food stimuli in the prefrontal cortex. Molecular Metabolism. 2014; 3(2):109–13. DOI: 10.1016/j.molmet.2013.11.009 [PubMed: 24634816]
84. Sevgi M, Rigoux L, Kuhn AB, Mauer J, Schilbach L, Hess ME, et al. An Obesity-Predisposing Variant of the FTO Gene Regulates D2R-Dependent Reward Learning. J Neurosci. 2015; 35(36): 12584–92. DOI: 10.1523/JNEUROSCI.1589-15.2015 [PubMed: 26354923]
85. Stice E, Yokum S, Bohon C, Marti N, Smolen A. Reward circuitry responsivity to food predicts future increases in body mass: moderating effects of DRD2 and DRD4. Neuroimage. 2010; 50(4): 1618–25. DOI: 10.1016/j.neuroimage.2010.01.081 [PubMed: 20116437]
86. Stice E, Burger KS, Yokum S. Reward Region Responsivity Predicts Future Weight Gain and Moderating Effects of the TaqIA Allele. J Neurosci. 2015; 35(28):10316–24. DOI: 10.1523/JNEUROSCI.3607-14.2015 [PubMed: 26180206]
87. Sun X, Luquet S, Small DM. DRD2: Bridging the Genome and Ingestive Behavior. Trends Cogn Sci. 2017; 21(5):372–84. DOI: 10.1016/j.tics.2017.03.004 [PubMed: 28372879]
88. Kroemer NB, Small DM. Fuel not fun: Reinterpreting attenuated brain responses to reward in obesity. Physiol Behav. 2016; 162:37–45. DOI: 10.1016/j.physbeh.2016.04.020 [PubMed: 27085908]
89. Felsted JA, Ren X, Chouinard-Decorte F, Small DM. Genetically determined differences in brain response to a primary food reward. J Neurosci. 2010; 30(7):2428–32. DOI: 10.1523/JNEUROSCI.5483-09.2010 [PubMed: 20164326]
90. Stice E, Yokum S, Blum K, Bohon C. Weight gain is associated with reduced striatal response to palatable food. J Neurosci. 2010; 30(39):13105–9. [PubMed: 20881128]
91. Heni M, Kullmann S, Ahlqvist E, Wagner R, Machicao F, Staiger H, et al. Interaction between the obesity-risk gene FTO and the dopamine D2 receptor gene ANKK1/TaqIA on insulin sensitivity. Diabetologia. 2016; 59(12):2622–31. DOI: 10.1007/s00125-016-4095-0 [PubMed: 27600277]
92. Claussnitzer M, Dankel SN, Kim KH, Quon G, Meuleman W, Haugen C, et al. FTO Obesity Variant Circuitry and Adipocyte Browning in Humans. N Engl J Med. 2015; 373(10):895–907. DOI: 10.1056/NEJMoa1502214 [PubMed: 26287746]
93. Karra E, O'Daly OG, Choudhury AI, Yousseif A, Millership S, Neary MT, et al. A link between FTO, ghrelin, and impaired brain food-cue responsivity. J Clin Invest. 2013; 123(8):3539–51. DOI: 10.1172/JCI44403 [PubMed: 23867619]
94. McGue M, Osler M, Christensen K. Causal inference and observational research: The utility of twins. Persp Psychol Sci. 2010; 5(5):546–56.
*95. Doornweerd S, van Duinkerken E, de Geus EJ, Arbab-Zadeh P, Veltman DJ, RG IJ. Overweight is associated with lower resting state functional connectivity in females after eliminating genetic effects: A twin study. Hum Brain Mapp. 2017; 38(10):5069–81. Suggests that functional connectivity is altered in obesity, independent of genetics. DOI: 10.1002/hbm.23715 [PubMed: 28718512]
96. Robinson S, Basso G, Soldati N, Sailer U, Jovicich J, Bruzzone L, et al. A resting state network in the motor control circuit of the basal ganglia. BMC Neurosci. 2009; 10:137.doi: 10.1186/1471-2202-10-137 [PubMed: 19930640]

97. Schur EA, Kleinhans NM, Goldberg J, Buchwald DS, Polivy J, Del Parigi A, et al. Acquired differences in brain responses among monozygotic twins discordant for restrained eating. Physiol Behav. 2012; 105(2):560–7. DOI: 10.1016/j.physbeh.2011.09.008 [PubMed: 21945867]

98. Stratigopoulos G, Martin Carli JF, O'Day DR, Wang L, Leduc CA, Lanzano P, et al. Hypomorphism for RPGRIP1L, a ciliary gene vicinal to the FTO locus, causes increased adiposity in mice. Cell Metab. 2014; 19(5):767–79. DOI: 10.1016/j.cmet.2014.04.009 [PubMed: 24807221]

*99. Stratigopoulos G, Burnett LC, Rausch R, Gill R, Penn DB, Skowronski AA, et al. Hypomorphism of Fto and Rpgrip1l causes obesity in mice. J Clin Invest. 2016; 126(5):1897–910. Provides a potential molecular mechanism linking polymorphisms in *FTO* to hyperphagia and weight gain via impaired neuronal leptin signaling. DOI: 10.1172/JCI85526 [PubMed: 27064284]

Table 1

Twin study approaches

Twin approach	Design	Purpose
Classical twin study	Population-based sample of MZ and DZ pairs	Parse genetic, unique environmental, and family environment influences on a phenotype
Experimental MZ design	MZ only	Establish inherited basis for response to an environmental stimulus [29]
Co-twin control study	Discordant pairs, usually MZ only	Define the characteristics of a specific trait that are independent of genetics; evaluate for genetic confounding
Twin association studies	MZ and DZ pairs, or MZ only; often uses within-twin-pair differences as variables	Test if associations of risk factors with disease are independent of genetic, familial, and other factors using epidemiological approaches and regression modeling [30]

MZ=monozygotic; DZ=dizygotic