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Weighing the evidence: Variance in brain responses to milkshake receipt is predictive of eating behavior

Nils B. Kroemer [a,b,c,*], Xue Sun [a,d], Maria G. Veldhuizen [a,b], Amanda E. Babbs [a], Ivan E. de Araujo [a,b], Dana M. Small [a,b,c,d,e,**]

[a] The John B. Pierce Laboratory, New Haven, CT, 06519, USA
[b] Psychiatry Department, Yale University, New Haven, CT, 06519, USA
[c] Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, 01187 Dresden, Germany
[d] Yale Interdepartmental Neuroscience Program, Yale University, New Haven, CT, 06520, USA
[e] Department of Psychology, Yale University, New Haven, CT, 06520, USA

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ABSTRACT

Variations in brain responses to sensory stimuli are typically considered to lack information content and treated as "noise". Alternatively, variable response patterns may reflect the adjustment of biological parameters to external factors. We used functional magnetic resonance imaging in healthy non-dieting individuals to test whether intra-individual variation in brain response to the receipt of milkshake is associated with a range of behavioral and metabolic parameters. We found that, following a meal, high variability in nucleus accumbens (NAcc) response to milkshake is associated with higher body mass index, greater dietary disinhibition, more variable ad libitum food consumption, faster increases in plasma insulin, faster decreases in plasma glucose, and greater weight loss over 1 year. Our results thus uncover a series of physiological parameters encrypted as variable responses in NAcc to food stimuli. They also suggest that variations in striatal activity regulate the activation of behavioral and metabolic responses to food availability.

1. Introduction

Converging evidence suggests that variation in brain responses to the same stimulus contains important information independent of average signal amplitude (Garrett et al., 2013; Dinstein et al., 2015). This echoes one of the fundamental principles of biology, namely the law of variation. Populations are characterized by variation and variability is a prerequisite for adaptation. According to the Bayes optimality hypothesis, variability in neuronal responses may promote behavioral flexibility (Garrett et al., 2013). Evidently, if neurons fired in the same manner every time a specific stimulus was encountered (deterministically), adaptation to different circumstances such as metabolic state would be impossible. Hence, populations of neurons may effectively encode probability distributions of responses given the reliability of incoming signals and an optimal response can be chosen based on proximity of the stimulus to each neuron's preferred stimulus criterion. Therefore, the range of the observed brain response to food rewards may be indicative of the representational range of the stimulus in the brain, which in turn may help to predict certain aspects of eating behavior such as the range of caloric intake. In the current study, we sought to investigate whether intra-individual variability in brain response to a palatable and energy dense food is associated with physiological responses that reflect eating behavior, metabolic health, and susceptibility to weight gain.

Recent work suggests that variability in fMRI time series data may also contain critical information (Garrett et al., 2013; Dinstein et al., 2015). For example, variability in NAcc response to the same stimulus has recently been shown to reflect behavioral variability in approach and effort. Specifically, response to reward cues is predictive of instrumental motivation on a trial-by-trial basis, indicating that brain response in the NAcc may "fuel" approach behavior (Knutson et al., 2014; Kroemer et al., 2014). Notably, this approach tendency as encoded by NAcc may also impinge on rational behavior leading to disadvantageous decisions involving costly errors (Chumbley et al., 2014). This is consistent with current theories emphasizing the involvement of dopamine transmission in the NAcc with approach and incentive salience (Salamone and Correa, 2012; Floresco, 2015).

The possibility that NAcc variance may be associated with differences in approach behavior is of considerable interest to obesity research. Meta-analyses have shown that food cues, especially those depicting high-caloric food, reliably elicit activation in NAcc (van der Laan et al., 2011; Tang et al., 2012). However, despite reported

* Correspondence to: N.B. Kroemer, Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, 01187 Dresden, Germany.
** Correspondence to: D.M. Small, 290 Congress Ave., New Haven, CT 06519, USA.
E-mail addresses: nils.kroemer@yale.edu (N.B. Kroemer), dana.small@yale.edu (D.M. Small).

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associations with susceptibility to weight gain (Demos et al., 2012; Murdaugh et al., 2012; Geha et al., 2013), meta-analyses have failed to consistently observe differences in NAcc response between overweight/obese and normal-weight individuals (Ziauddeen et al., 2012; Brooks et al., 2013; García-García et al., 2014). Although it is possible that NAcc function contributes to food approach behavior without being consistently altered in overweight/obesity, an alternative explanation is that the average signal amplitude is not affected, but other characteristics of the signal such as variance might be. For example, high variability in the NAcc approach signal could lead to high variability in food intake leading to dietary disinhibition and overeating. Likewise, based on signal detection theory, a more variable approach signal of the same amplitude could be less effective in driving behavioral approach, which would reduce the reinforcement value of food and may facilitate weight loss.

Given that inter-individual variation in NAcc response is implicated in variations in appetitive behavior and that intra-individual fluctuations in NAcc responses predict fluctuations in behavioral approach, we tested the prediction that inter-individual differences in intra-individual variability in NAcc response to a palatable and energy dense milkshake would be associated with body weight, metabolic health and eating behavior. We hypothesized that variability would be associated with body weight regulation as indicated by the multivariate outcome BMI and changes in BMI after 1 year of follow-up. In particular, we hypothesized that high variability in the NAcc would be positively associated with body weight. We reasoned that the range in food intake would be increased in overweight/obese individuals because of the reported associations with restraint (which could introduce attenuated brain response at the lower end) and disinhibition (which could introduce stronger brain response at the upper end of the distribution). In contrast, we predicted that variance in the oral sensory cortex of the dorsal mid insula (Veldhuizen et al., 2011) would not be associated with our outcome measures. Whereas the insula is essentially involved in taste processing and has been linked to obesity in previous studies (Brooks et al., 2013), signal variability in the insula is not known to map onto fluctuations in approach behavior. Due to the important role of the insula during the task, it provides a good second candidate region to test the specificity of signal fluctuations in the NAcc on body weight regulation.

2. Materials and methods

2.1. Participants

A total of 34 right-handed participants (16 male; $M_{age} = 25.9$ years, $SD = 6.0$, range 18–40) were recruited from the greater New Haven area through the Yale University Interdisciplinary Research Consortium on Stress, Self-Control and Addiction (IRCSSA) P30 Subject's core and via flyer advertisement. Two subjects were excluded from the 1-year follow-up analysis (one did not complete follow-up, one started psychiatric medication in the interim between initial testing and follow-up). All participants were screened over the phone to be 40 years or less of age, free of psychiatric disorders, eating disorders, current dieting behavior, alcoholism, use of tobacco or drugs other than alcohol, history of head injury with loss of consciousness, use of daily medication other than monophasic birth control, chemosensory impairments, lactose intolerance or food allergies. As our aim was to sample across a representative healthy Western population, participant BMIs ranged from normal to obese ($M_{BMI} = 25.3$ kg/m^2, $SD = 4.4$, range 19.5–37.0) and no upper limit on BMI was imposed on recruitment, as long as the participant was comfortable in the MRI scanner with our stimulus delivery equipment. Participants were also free of self-reported obesity-related health issues such as diabetes. All participants provided written informed consent at their first lab visit and the study was approved by the Yale Human Investigations Committee.

2.2. Procedure

The overall procedure of the study has been reported in detail before (Sun et al., 2014, 2015) and is briefly summarized here (for details, see supporting information). Participants took part in one fMRI training session, three fMRI scanning sessions (hungry, fixed meal and ad libitum conditions), and one behavioral test session. Lunch on the fixed and ad libitum scan days consisted of apple slices (approximately 25 kcal of apple per serving) and their choice of sandwich. Each sandwich was designed to contain approximately 400 kcal and was cut into quarters before serving. During scanning participants received .5 ml of milkshake or tasteless solution over 4 s delivered via a portable gustometer system and dripped from the mouthpiece onto the tongue each 20 times in total per condition (Veldhuizen et al., 2007). In order to minimize sensory adaptations to repeated presentations of milkshake stimuli, two different flavors of milkshake (chocolate and strawberry) were presented in an interleaved order. Ad libitum intake was also assessed following each scanning session. Participants received the milkshakes in large opaque cups with translucent lids and a large bowl of prepared cheese pasta totaling approximately 1750 kcal.

At the behavioral test session, a variation of Epstein's Behavioral Choice Task (BCT) was administered that was configured to assess the relative reinforcing value of food (Saelens and Epstein, 1996; see supporting information). Height and weight were also measured and BMI calculated. All sessions were conducted on separate days within 3 months and scan order was counterbalanced ($M_{delay} = 22.8$ days). On the morning of the fMRI visit, participants ate breakfast bars (1 package for women, 1.5 packages for men) and were instructed to refrain from eating or drinking (except for water) until their session that began at 12:15 pm.

During fMRI scan sessions, participants repeatedly rated hunger and fullness (for results, see Sun et al., 2015). After arriving at the study center, a Teflon catheter was inserted into an antecubital vein for blood sampling and IV blood draws occurred concomitant to internal state ratings. After two baseline blood draws, participants ate either a fixed-portion meal (at the fixed meal scan day, consisting of 1 sandwich and 1 serving of apple slices for women, 1.5 sandwiches and 1 serving of apple slices for men), an ad libitum meal (at the sated scan day; 3 sandwiches and 4 servings of apple slices for both women and men and instructed to "eat as much as they'd like") or nothing (at the hungry scan day). Participants then rated hunger and fullness and were taken to the scanner, outfitted with the stimulus delivery devices, and inserted into the bore. In total, two baseline blood samples were obtained and three more samples were obtained 30, 60, and 90 min after receiving the meal (for fixed meal and satiety conditions). After participants were removed from the scanner, they were taken to a behavioral testing room where they were presented with both flavors of milkshake followed by the bowl of cheese pasta and instructed to eat ad libitum from both. Milkshake and pasta intake were recorded without the participants' knowledge by weighing before and after consumption and converted to kilocalories using information provided on the nutritional facts labels by the manufacturers.

Participants returned to the lab as close as possible to 1 year from the exact date that their initial anthropometric measurements were taken ($M_{delay} = 53.0$ weeks, $SD = 3.0$). Two participants who had moved away from New Haven and were unable to return were instructed to weigh themselves on a digital scale with minimal clothing and self-report their new weight via e-mail. One participant's follow-up data on weight change was excluded because of onset of long-term medication that is commonly associated with weight gain and another participant did not provide follow-up data ($N = 32$ for ΔBMI; Sun et al., 2015). The Three-Factor Eating Questionnaire (TFEQ; Stunkard and Messick, 1985) was collected at follow-up as well ($N = 31$). For the multivariate analyses involving BMI and change in BMI (ΔBMI = $BMI_{T2} - BMI_{T1}$; positive numbers reflect weight gain), we assessed all available data (see supporting information).

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