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Effects of 3-week total meal replacement vs. typical food-based diet on human brain functional magnetic resonance imaging food-cue reactivity and functional connectivity in people with obesity

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ABSTRACT

Objectives: Calorie restriction via total meal replacement (TMR) results in greater reduction of food cravings compared to reduced-calorie typical diet (TD). Direct evidence of the impact of these interventions on human brain fMRI food-cue reactivity (fMRI-FCR) and functional connectivity is absent. We examined the effects of a 3-week 1120 kcal/d TMR intervention as compared to an iso-caloric TD intervention using an fMRI-FCR paradigm.

Methods: Thirty-two male and female subjects with obesity (19–60 years; 30–39.9 kg/m^2) participated in a randomized two-group repeated measures dietary intervention study consisting of 1120 kcal/d from either 1) TMR (shakes), 2) TD (portion control). Pre-intervention and following the 3-week diet fMRI-FCR, functional connectivity, food cravings (Food Craving Inventory) and weight were considered.

Results: Compared to TD, TMR showed increased fMRI-FCR of the bilateral dorsolateral prefrontal (dlPFC), orbitofrontal, anterior cingulate, primary motor and left insular cortices and bilateral nucleus accumbens regions in the post-intervention state relative to the pre-intervention state. Compared to TD, TMR was also associated with negative modulation of fMRI-FCR of the nucleus accumbens, orbitofrontal cortex and amygdala by dlPFC. Reduced body weight (4.87 kg, $P < 0.001$), body fat (2.19 kg, $P = 0.004$) and overall food cravings (0.41, $P = 0.047$) were seen in the TMR group. In the TD group reduced body weight (2.37 kg, $P = 0.004$) and body fat (1.64 kg, $P = 0.002$) were noted. Weight loss was significantly greater in TMR versus TD (2.50 kg, $P = 0.007$).

Conclusions: Greater weight loss and reduced cravings, coupled with stronger activations and potential negative modulation of the food reward related regions by the dlPFC during exposure to visual food cues is consistent with increased executive control in TMR vs. TD.

1. Introduction

Prevalence of over-weight and obesity are rising worldwide (Ng et al., 2014). Extended calorie restriction (ECR) is often used for weight loss (Finer, 2001; Franz et al., 2007). Several studies have described reduced food cravings and food-related reward expectancy following ECR (Harvey, Wing, & Mullen, 1993; Martin, O'Neil, & Pawlow, 2006, 2011). Moreover, it has been demonstrated that ECR via liquid formula-based total meal replacement (TMR) very low-calorie diet suppresses food cravings to a greater extent compared to ECR via a typical food-based low-calorie diet (TD) (Martin et al., 2006).

Our recent review (Kahathuduwa, Boyd, Davis, O'Boyle, & Binks, 2016), noted there is little research directly examining human brain functional magnetic resonance imaging food-cue reactivity (fMRI-FCR) involving ECR, as most studies focus on total fasting (typically

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List of abbreviations

ACC	anterior cingulate cortex
BF	body fat
BL	baseline of fMRI signal
COPEs	contrasts of parameter estimates
dlPFC	dorsolateral prefrontal cortex
ECR	extended calorie restriction
FCI	Food Craving Inventory
fMRI	functional magnetic resonance imaging
FSL	FMRIB Software Library
NAcc	nucleus accumbens
NS	not significant
OFC	orbitofrontal cortex
PCG	precentral gyrus
ROIs	regions of interest
TMR	total meal replacement
TD	typical diet
VAS	visual analogue scales
vmPFC	ventromedial prefrontal cortex

24–48 h). Evidence suggests that ECR may be associated with decreased food-cue reactivity in brain regions regulating energy balance (e.g. hypothalamus (Rosenbaum, Sy, Pavlovich, Leibel, & Hirsch, 2008)), some regions of the dopaminergic reward system (e.g. orbitofrontal cortex (Bruce et al., 2014; Rosenbaum et al., 2008), anterior cingulate cortex (Murdaugh, Cox, Cook, & Weller, 2012; Rosenbaum et al., 2008) amygdala (Rosenbaum et al., 2008)), nucleus accumbens (Avena, Murray, & Gold, 2013) and regions that execute ingestive behavior (e.g. precentral gyrus (Rosenbaum et al., 2008)). This decrease in reactivity in the dopaminergic reward system, homeostatic regions, and regions associated with ingestion from ECR is frequently accompanied by increased activation in the middle frontal gyrus (i.e. dorsolateral prefrontal cortex) (Rosenbaum et al., 2008). This has been interpreted as indicating greater executive control over ingestion and food cravings.

However, several gaps in understanding of the neurophysiological and behavioral effects of ECR remain. First, changes in fMRI-FCR in the context of ECR have not been prospectively examined in a randomized controlled trial (Kahathuduwa et al., 2016). Second, even though evidence suggests that ECR suppresses food cravings and fMRI-FCR in several brain regions that process food-related stimuli and reward, the precise nature of the neurophysiological mechanisms involved are unknown. Third, exploring functional connectivity using psychophysiological interaction (PPI) analysis could lead to the identification of potential mechanisms linking brain regions that are associated with decreased food cravings observed in relation to ECR. While the dorsolateral prefrontal cortex has often been assumed to be exerting executive control over ingestion, the effects of ECR-associated suppressive relationships between the dorsolateral prefrontal cortex and the reward-related brain regions have not been studied to-date. Finally, even though previous evidence suggested that a very low-calorie diet implemented via liquid formula-based TMR seems to be superior to a low-calorie diet implemented via TD in suppressing food cravings, effects of these interventions on food cravings, fMRI-FCR and functional connectivity between the dorsolateral prefrontal cortex and the food reward-related regions of the brain have not been delineated in a randomized controlled trial.

Therefore, we examined whether participation by subjects with obesity (BMI 30–39.9 kg/m^2) in a 3-week isocaloric, low calorie (1120 kcal/day) diet derived from TMR versus TD will have differential effects on functional activations (i.e. BOLD responses) in brain regions that influence ingestive behavior. We hypothesized that a significant group (i.e. TMR versus TD) X time (i.e. pre- vs. post-intervention) interaction and a significant main effect for time would be seen in the fMRI-FCR of the brain regions that are thought to regulate executive control over ingestion (i.e. dorsolateral prefrontal cortex) and brain regions that have been associated with food reward (i.e. orbitofrontal cortex, anterior cingulate cortex, amygdala, precentral gyrus and the nucleus accumbens). While direct evidence was not available regarding the possible role of the insula in fMRI-FCR, considering that one of its functions includes regulating pleasure associated with ingestion (Berridge, 2009), we anticipated that the fMRI-FCR of the insula would also decrease with ECR as would other food reward and pleasure-related regions (Kahathuduwa et al., 2016). We specifically hypothesized *a priori*, an increase in fMRI-FCR compared to pre-intervention state in the dorsolateral prefrontal cortex in both groups, with fMRI-FCR of the TMR group being greater than the TD group. We also predicted a decline in fMRI-FCR in all hypothesized food reward, and pleasure-related regions and brain regions that regulate motor readiness to ingest, with a greater decline in TMR versus TD. In relation to the functional connectivity analyses, we hypothesized that in a post- vs. pre-intervention comparison, the fMRI-FCR of bilateral dorsolateral prefrontal cortices will be negatively associated with fMRI-FCR of the brain regions that regulate food reward (i.e. bilateral nucleus accumbens, orbitofrontal cortex, insula, amygdala and anterior cingulate cortex) and motor responses in relation to ingestion (i.e. the precentral gyrus) 1) in the TMR group when compared with the TD group; and 2) in a pooled analysis of TMR and TD groups (i.e. independent influence of ECR). Finally, with regard to self-reported food cravings, we hypothesized that compared to TD, TMR would be associated with a significant reduction of overall food cravings as well as cravings for sweet food, high-fat food, starchy food and fast food as measured by the Food Craving Inventory (White, Whisenhunt, Williamson, Greenway, & Netemeyer, 2002).

2. Methods

2.1. Ethics

The TTU Human Research Protection Program approved the study (TTU IRB #505380). All procedures were conducted in accordance with the Helsinki Declaration amended in 2000 (WHO, 2001). Informed written consent was obtained from all subjects who met eligibility criteria.

2.2. Subjects

Thirty-two adult men and women with obesity (age 19–60 years; BMI 30–39.9 kg/m^2) were enrolled from January through June 2016. Potential subjects were screened to determine eligibility via telephone. Subjects were excluded based on the following: contraindications for magnetic resonance imaging; gross visual, auditory or motor impairments; medical contraindications (e.g. diabetes mellitus, uncontrolled hypertension), neurological or severe psychiatric conditions; recent (3 months) weight loss program or ever had bariatric surgery; diagnosed eating disorders; taking medications that may affect fMRI-FCR; current smokers; and unwilling to undergo a 3-week diet. Eligible subjects attended an in-person assessment (visit 1). Pre-menopausal women were scheduled for visit 2 during the second half of the follicular phase of their menstrual cycle (i.e. day 10–14). This allowed for scheduling visit 5 within the follicular phase of the subsequent menstrual cycle (i.e.