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Interactions between neural decision-making circuits predict long-term dietary treatment success in obesity

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A B S T R A C T

Although dietary decision-making is regulated by multiple interacting neural controllers, their impact on dietary treatment success in obesity has only been investigated individually. Here, we used fMRI to test how well interactions between the Pavlovian system (automatically triggering urges of consumption after food cue exposure) and the goal-directed system (considering long-term consequences of food decisions) predict future dietary success achieved in 39 months. Activity of the Pavlovian system was measured with a cue-reactivity task by comparing perception of food versus control pictures, activity of the goal-directed system with a food-specific delay discounting paradigm. Both tasks were applied in 30 individuals with obesity up to five times: Before a 12-week diet, immediately thereafter, and at three annual follow-up visits. Brain activity was analyzed in two steps. In the first, we searched for areas involved in Pavlovian processes and goal-directed control across the 39-month study period with voxel-wise linear mixed-effects (LME) analyses. In the second, we computed network parameters reflecting the covariation of longitudinal voxel activity (i.e. principal components) in the regions identified in the first step and used them to predict body mass changes across the 39 months with LME models. Network analyses testing the link of dietary success with activity of the individual systems as reference found a moderate negative link to Pavlovian activity primarily in left hippocampus and a moderate positive association to goal-directed activity primarily in right inferior parietal gyrus. A *cross-paradigm* network analysis that integrated activity measured in both tasks revealed a strong positive link for interactions between visual Pavlovian areas and goal-directed decision-making regions mainly located in right insular cortex. We conclude that adaptation of food cue processing resources to goal-directed control activity is an important prerequisite of sustained dietary weight loss, presumably since the latter activity can modulate Pavlovian urges triggered by frequent cue exposure in everyday life.

1. Introduction

Obesity is an epidemic that affects millions of people worldwide and that has substantial medical consequences, including cardiovascular disease, diabetes, and cancer (Ng et al., 2014; Schienkiewitz et al., 2012). Obesity involves a dysregulation of food intake (Bryant et al., 2008),

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which is controlled by an interplay of multiple neural decision-making (DM) systems (Rangel, 2013; Crombag et al., 2008; Dayan and Seymour, 2008; Lovibond, 1983; Williams and Williams, 1969; Brown and Jenkins, 1968). These neural systems include Pavlovian and goal-directed controllers.

Pavlovian controllers trigger simple, stereotypical behaviors in response to stimuli. A typical example is the salivation response of a dog when confronted with food. Pavlovian responses can also be triggered by novel stimuli if these are predictive of a reward (Rangel, 2013; Dayan and Seymour, 2008). In this framework, cues predictive of (food) reward can acquire motivational characteristics similar to those of the reinforcers and thus trigger consumption (Robbins et al., 2008). A variety of studies have suggested that this motivational mechanism (frequently referred to as 'food wanting') is mediated by activity of the brain reward system and connected areas including the striatum, orbitofrontal (OFC) and anterior cingulate cortex (ACC), hippocampus, and fusiform gyrus (Volkow et al., 2017; Rypma et al., 2015; Jiang et al., 2015; Castro and Berridge, 2014; Rangel, 2013; Berridge et al., 2009; Ito et al., 2005). Consistently, studies using cue-reactivity tasks that were developed to measure this mechanism by contrasting pictures of food and control stimuli found that persons with obesity showed stronger food-cue specific responses in these areas than healthy controls (Martin et al., 2010; Stoeckel et al., 2008; Rothemund et al., 2007). Moreover, this hyperresponsivity is associated with less favorable body weight development across a twelve-month period (Kahathuduwa et al., 2018; Murdaugh et al., 2012; Stice et al., 2010).

Pavlovian responses are triggered automatically by stimuli and thus do not take any future side effects of behavior into account. A second, goal-directed DM system is responsible for action plans that consider future consequences. When confronted with different behavioral options, the goal-directed system compares the values for the options based on a model that reflects the probability that an action will lead to a specific outcome (Rangel, 2013). For example, this system could consider that a continuous intake of high-calorie food items can lead to undesirable body weight increases and thus inhibit the impulse to eat. The goal-directed system is typically studied using delay discounting tasks, where participants are required to exert goal-directed control by delaying the receipt of a rewarding stimulus to obtain a larger reward in the future. Delay discounting has revealed a network of brain regions underlying goal-directed control, including dorsolateral prefrontal (DLPFC) and ventromedial prefrontal cortex (VMPFC), parietal and insular areas (e.g. Guo and Feng, 2015; Rangel, 2013; McClure et al., 2004). Activity in the DLPFC measured with this task is positively linked to behavioral impulse control (Weygandt et al., 2013; Hare et al., 2009) and favorable weight development across time (Weygandt et al., 2015, 2013; Kishinevsky et al., 2012; see McClelland et al., 2016 for an overview).

Together, the existing neuroimaging studies provided valuable insights into neural mechanisms of obesity and body mass development (e.g. Weygandt et al., 2015, 2013; Kishinevsky et al., 2012; Murdaugh et al., 2012; Martin et al., 2010; Stice et al., 2010; Stoeckel et al., 2008; Rothemund et al., 2007) by either analyzing Pavlovian or goal-directed DM systems. However, a substantial number of findings suggest that dietary DM is also influenced by the interplay between these systems. For example, inhibitory interactions have been found by animal studies showing that pigeons do not learn to refrain from pecking an anticipatory Pavlovian food stimulus when refraining is rewarded (Williams and Williams, 1969). Moreover, modulatory interactions were demonstrated by studies showing that anticipatory Pavlovian stimuli strengthen the instrumental responses to discriminative stimuli when co-occurring in the instrumental context (e.g. Crombag et al., 2008; Lovibond, 1983). Please see Rangel (2013) for an overview on dietary DM and Tops et al. (2017) for a more generic model of interactions between neural systems involved in self-regulation.

Inspired by these findings, we aimed to investigate the impact of interactions between Pavlovian and goal-directed DM systems on the clinically most important treatment outcome in obesity – long-term maintenance of dietary weight loss (e.g., Sjöström et al., 1998; Wadden et al., 1998; Brownell and Wadden, 1992). To achieve this goal, we utilized fMRI data measured in 30 persons with obesity at up to five time points with a cue-reactivity and a delay discounting paradigm across the full 39-month period of a clinical research project comprising a weight reduction and a subsequent weight maintenance stage. This was done in four longitudinal fMRI analyses using linear mixed-effects (LME) regression. In the first two, we searched for brain regions showing two types of obesity-related Pavlovian responses. Specifically, given that persons with obesity show increased food wanting due to a hyper-responsivity of the reward system to food cues (i.e., 'anticipatory reward surfeit'; Adise et al., 2018; Kroemer and Small, 2016; Val-Laillet et al., 2015; Berridge et al., 2009), we searched for areas responding stronger to high-caloric food than neutral control pictures in a stable fashion across all time points in the cue-reactivity task in Analysis 1. However, given that participation in a weight-reduction program could also function as Pavlovian extinction learning since food cues become less frequently coupled to reward (e.g. Peters et al., 2009), we additionally searched for regions showing a neural response decline across the study period in Analysis 2. Given that existing cue-reactivity obesity studies (e.g. Murdaugh et al., 2012; Stice et al., 2010; Martin et al., 2010; Stoeckel et al., 2008; Rothemund et al., 2007) are not conclusive with regard to the question of whether Pavlovian responses will be stable or weakening across the course of a combined weight reduction and maintenance program, we expected that striatum, OFC, ACC, hippocampus, and fusiform gyrus could be either found in Analysis 1 or 2. In Analysis 3, we aimed to identify brain regions responding stronger during difficult than easy food decisions in the delay discounting task in a stable fashion across the study period to identify brain regions involved in goal-directed DM. In line with a neuroeconomic model of goal-directed dietary DM (Rangel, 2013), we expected to find VMPFC, DLPFC, inferior parietal cortex, pre-SMA, precentral gyrus, and insular cortex in Analysis 3. Finally, in Analysis 4 we used activity in regions identified in Analyses 1 to 3 to model dietary success obtained across the 39-month period and related dietary variables. This was done based on network parameters reflecting the covariation of longitudinal voxel activity (i.e. principal components; PCS) computed separately for each of the three individual DM systems found in Analyses 1 to 3 as well as based on parameters reflecting the interaction between these systems. Due to the high importance of DLPFC for goal-directed decision-making and striatal regions for Pavlovian responses (Rangel, 2013), we hypothesized that interactions between these two regions would have a strong impact on future dietary weight loss in Analysis 4. For modelling based on individual systems, we hypothesized to identify the areas also assumed to be involved in Analyses 1–3.

2. Materials and methods

2.1. Participants

Acquisition of participants and measurements conducted in the present functional neuroimaging study (which is referred to as 'fMRI study' in the following) were partially coupled to the procedures of a study performed by the Clinic of Endocrinology, Diabetes and Metabolism at Charité – Universitätsmedizin Berlin (referred to as 'weight loss study' in the following). In the weight loss study (Mai et al., 2018; Brachs et al., 2016), individuals with obesity first participated in a twelve-week weight loss diet and were then randomly assigned to an intervention or *ad-libitum* group given they lost at least 8% body weight during the diet (see below for details on the diet and weight maintenance program). The weight loss study comprised four longitudinal measurement time points (i.e. preceding the twelve-week diet [T-3], immediately thereafter [T0], and twelve [T12] and 18 months after the end of a diet). In the fMRI study, participants were scanned at T-3, T0, T12, and additionally 24 (T24) and 36 months (T36) after the diet. Please note that this schedule defined on a monthly scale could slightly vary by some days in the fMRI study in practice due to organizational reasons. After application of