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Research report

Failing to learn from negative prediction errors: Obesity is associated with alterations in a fundamental neural learning mechanism

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ABSTRACT

Prediction errors (PEs) encode the difference between expected and actual action outcomes in the brain via dopaminergic modulation. Integration of these learning signals ensures efficient behavioral adaptation. Obesity has recently been linked to altered dopaminergic fronto-striatal circuits, thus implying impairments in cognitive domains that rely on its integrity.

28 obese and 30 lean human participants performed an implicit stimulus-response learning paradigm inside an fMRI scanner. Computational modeling and psychophysiological interaction (PPI) analysis was utilized for assessing PE-related learning and associated functional connectivity. We show that human obesity is associated with insufficient incorporation of negative PEs into behavioral adaptation even in a non-food context, suggesting differences in a fundamental neural learning mechanism. Obese subjects were less efficient in using negative PEs to improve implicit learning performance, despite proper coding of PEs in striatum. We further observed lower functional coupling between ventral striatum and supplementary motor area in obese subjects subsequent to negative PEs. Importantly, strength of functional coupling predicted task performance and negative PE utilization.

These findings show that obesity is linked to insufficient behavioral adaptation specifically in response to negative PEs, and to associated alterations in function and connectivity within the fronto-striatal system. Recognition of neural differences as a central characteristic of obesity hopefully paves the way to rethink established intervention

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strategies: Differential behavioral sensitivity to negative and positive PEs should be considered when designing intervention programs. Measures relying on penalization of unwanted behavior may prove less effective in obese subjects than alternative approaches.

1. Introduction

Human obesity has recently been associated with dynamic alterations within the dopaminergic pathways of the brain (Cosgrove, Veldhuizen, Sandiego, Morris, & Small, 2015; Guo, Simmons, Herscovitch, Martin, & Hall, 2014; Horstmann, Fenske & Hankir, 2015; Kessler, Zald, Ansari, & Cowan, 2014; van der Zwaal et al., 2016). The dopaminergic system is a key player in learning and adaptive behavior (Bayer & Glimcher, 2005; Cools et al., 2009; van der Schaaf et al., 2014). Thus, changes in dopaminergic transmission associated with obesity might offer a mechanistic explanation of observed impairments in learning and adaptive behavior (Coppin, Nolan-Poupart, Jones-Gotman, & Small, 2014; Horstmann, Dietrich, et al., 2015).

Learning in an uncertain environment is driven by the deviation between our prediction about the outcome of an action and the actual outcome. If the outcome is incongruent with the prediction, most probably behavior has to be adapted and predictions have to be updated. On the neural level, incongruity is paralleled by a prediction error (PE) signal in dopaminergic structures of the midbrain and relayed from there to striatal and prefrontal target regions to drive learning (Schultz, 2002; Schultz, Dayan, & Montague, 1997). A positive PE signals that the outcome is better than predicted, and a negative PE reveals that it is worse than expected. In rats, extracellular dopamine release in dopaminergic target regions such as the ventral striatum encode both positive and negative PEs on a common scale (Hart, Rutledge, Glimcher, & Phillips, 2014). In humans, both positive and negative PEs are reflected in changes of blood oxygen level dependent (BOLD) activation within striatum (D'Ardenne et al., 2008; McClure, Berns, & Montague, 2003; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006).

Dopamine mediates learning from positive as well as negative outcomes (Mathar et al., 2017; van der Schaaf et al., 2014), but via two segregated ('direct'/'indirect') pathways (Cox et al., 2015; Frank, 2005; Frank & O'Reilly, 2006; Kravitz et al., 2010). It has been suggested that obesity is predominantly associated with alterations that affect the dopamine receptor D2 dependent 'indirect pathway' (Horstmann, Fenske, et al., 2015). In the 'indirect pathway' (Gerfen et al., 1990; Surmeier, Ding, Day, Wang, & Shen, 2007), postsynaptic D2 receptors are sensitive to detecting transient dips within the tonic DA signal (Day et al., 2006; Goto & Grace, 2005). Hence, wrong stimulus-response associations are weakened through D2 receptor activity in the indirect pathway subsequent to negative PEs (Jocham et al., 2009, 2014; Klein et al., 2007). Importantly, changes in the indirect pathway may therefore alter learning from negative PEs in particular.

Similar to findings in alcohol and nicotine addiction (Chiu, Lohrenz, & Montague, 2008; Park et al., 2010), obese subjects might fail to use negative PE-signals in particular to adjust their eating behavior efficiently and thus exhibit uncontrolled, habit-like eating patterns (de Jong, Meijboom, Vanderschuren, & Adan, 2013; Horstmann, Dietrich, et al., 2015; Janssen et al., 2016). A deficiency in incorporating negative PEs into guidance of subsequent behavior might be a mechanism sustaining obesity and, importantly, might also pertain to general implicit learning behavior beyond the food reward context. This deficiency may either result from insufficient coding of PEs or from diminished transmission of this learning signal to higher cortical areas involved in behavioral adaptation.

Here, we tested the hypothesis that obesity is associated with a deficiency in incorporating negative PEs into guidance of subsequent behavior during implicit learning in a non-food context. Lean and obese subjects performed the Weather Prediction Task (WPT) (Knowlton, Squire, & Gluck, 1994) in an fMRI setting. Successful performance in this task heavily depends on dopaminergic transmission, formation and updating of predictions, and the utilization of positive and negative PE-signals in subsequent adaptation of response behavior (Mathar et al., 2017). It has been previously used to study PE-related brain activity (Rodriguez, Aron, & Poldrack, 2006) and associated dopaminergic transmission (Jahanshahi et al., 2010; Mathar et al., 2017; Wilkinson et al., 2014). We hypothesized an obesity-specific impairment in using negative PEs for successful adaptation of behavior.

2. Material and methods

2.1. Subjects

The study was carried out in compliance with the Declaration of Helsinki and approved by the local ethics committee of the University of Leipzig. We included 58 healthy Caucasian participants. Subjects were separated into two groups according to their BMI: an obese group (BMI $\geq$ 30, BMI < 40), consisting of 28 (15 female) subjects, and a lean control group (BMI $\geq$ 19, BMI $\leq$ 25), consisting of 30 (15 female) subjects, respectively. Groups of lean and obese subjects were closely matched for gender, age and educational background (Table 1). To rule out that obesity-associated findings may be confounded by group differences regarding IQ or working memory capacity, we administered two short standard IQ tests (Formann & Piswanger, 1979; Lehrl, 1989) and a two-back task post-hoc in a subsample of 47 participants (Table 1). All groups showed comparable performance. All participants were right-handed (Edinburgh Handedness Inventory (Oldfield, 1971)) and between 18 and 35 years old. Exclusion criteria were hypertension, dyslipidemia, metabolic syndrome, depression