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Hunger and disinhibition but not cognitive restraint are associated with central norepinephrine transporter availability

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ABSTRACT

The relationship between food-intake related behaviours measured by the Three-Factor Eating Questionnaire (TFEQ) and *in vivo* norepinephrine transporter (NET) availability has not been explored yet. We investigated ten obese individuals (body mass index (BMI) 42.4 ± 3.7 kg/m^2) and ten normal-weight healthy controls (HC, BMI 23.9 ± 2.5 kg/m^2) with (*S,S*)-[^{11}C]-O-methylreboxetine ([^{11}C]MRB) positron emission tomography (PET). All participants completed the TFEQ, which measures cognitive restraint, disinhibition and hunger. Image analysis required magnetic resonance imaging data sets onto which volumes-of-interests were drawn. Tissue time activity curves (TACs) were obtained from the dynamic PET data followed by kinetic modeling of these regional brain TACs applying the multilinear reference tissue model (2 parameters) with the occipital cortex as reference region.

Obese individuals scored significantly higher on the hunger subscale of the TFEQ. Correlative data analysis showed that a higher degree of hunger correlated negatively with the NET availability of the insular cortex in both obese individuals and HC; however, this finding was more pronounced in obesity. Further, for obese individuals, a negative correlation between disinhibition and NET BP_{ND} of the locus coeruleus was detected.

In conclusion, these initial data provide *in vivo* imaging support for the involvement of the central NE system in maladaptive eating behaviors such as susceptibility to hunger.

1. Introduction

Assessment of eating behaviors has been applied to obesity research to evaluate potential contributing factors to this major, rapidly developing epidemic (Witten, 2016). The Three-Factor Eating Questionnaire (TFEQ) (Stunkard & Messick, 1985), a widely used self-report questionnaire, has been extensively used in the study of eating behaviours, measuring the constructs of cognitive restraint, disinhibition and hunger. In short, cognitive restraint of eating is defined as the degree of cognitive control in daily food intake; disinhibition is the loss of control in food intake; and hunger is described as the susceptibility for internal or external hunger signs. Lately, in a growing body of neuroimaging literature, those behavioral aspects of eating have been further elucidated. Research on structural brain alterations demonstrated a close link between eating behaviors measured by the TFEQ and brain areas involved in homeostatic keeping, habitual learning and cognitive control of food intake (Yao, Li, Dai, & Dong, 2016). In fact, higher cognitive restraint correlated positively with the gray matter volume (GMV) of a cognitive-control associated brain region, the dorsolateral prefrontal cortex (DLPFC). Inversely, higher disinhibition has been linked to lower middle frontal gyrus volume (Yao et al., 2016), lower orbitofrontal cortex volume and executive dysfunction (Maayan, Hoogendoorn, Sweat, & Convit, 2011). Susceptibility to hunger has also been found to negatively correlate with the middle frontal gyrus volume (Yao et al., 2016), which suggests an impaired cognitive control element for higher levels of

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Abbreviations

BMI	body mass index
BP_{ND}	binding potential
DLPFC	dorsolateral prefrontal cortex
fMRI	functional magnetic resonance imaging
GMV	gray matter volume
HC	healthy controls
MRI	magnetic resonance imaging
MRTM	multilinear reference tissue model
NE	norepinephrine
NET	norepinephrine transporter
PET	positron emission tomography
[^{11}C]MRB	(*S,S*)-[^{11}C]-O-methylreboxetine
TFEQ	Three-Factor Eating Questionnaire

both hunger and disinhibition.

Further, the TFEQ has been utilized to study eating behaviours in relation to pharmacological obesity treatment, including the assessment of phentermine, which is an anorectic agent acting as a potent substrate at the norepinephrine transporter (NET) promoting its release (Skopp & Jantos, 2013). To that effect, it has been shown that greater hunger and less cognitive restraint predict weight loss success with phentermine treatment (Thomas et al., 2016), but further data are scarce in this regard. Yet, with the recent introduction of suitable NET-selective radiotracers, it has been possible to examine *in vivo* NET availability (Ding et al., 2003). However, the relationship between food intake-related behaviour measured by means of the TFEQ and *in vivo* NET availability has not been explored yet. Hence, the current analysis was designed to fill this gap in the literature. We investigated the TFEQ data from a recently published cohort of ten obese and ten non-obese healthy controls (HC) that underwent (*S,S*)-[^{11}C]-O-methylreboxetine ([^{11}C]MRB) positron emission tomography (PET) to explore whether central *in vivo* NET availability is linked to the degree of cognitive restraint, disinhibition and hunger. Following the observations made above, cognitive control may be a key element among the investigated eating behaviours. As such, we investigated whether eating behaviours with an impaired cognitive control level (disinhibition and hunger) share a similar *in vivo* NET distribution pattern in affiliated brain areas (e.g. DLPFC, prefrontal cortex, orbitofrontal cortex). Next to the cognitive control over food we investigated regions associated with processing external sensory information (e.g. insula, thalamus).

2. Subjects

Details of the participants have been reported (Bresch et al., 2017; Hesse et al., 2017). In this pilot study, ten obese (6 women, aged 34.4 ± 9.0 years, BMI 42.4 ± 3.7 kg/m^2) and ten non-obese HC (6 women, aged 33.3 ± 10.0 years, BMI 23.9 ± 2.5 kg/m^2) participated. Briefly, exclusion criteria were current or past neurological or psychiatric illness; positive family history for psychiatric illnesses; former psychotherapy; resistant hypertension; insulin-dependent diabetes, or other medical conditions that may alter brain function; the use of central-acting drugs; participation in weight loss programs during the last 6 months; past or present history of alcohol misuse and/or illicit drug abuse; contraindications for magnetic resonance imaging (MRI, e.g. implanted ferromagnetic devices, claustrophobia); pregnancy or breast feeding. The study was approved by the ethics committee of the Medical Faculty of the University of Leipzig (IFB PET K7-7, EC number 206-10-08032010) and by the Federal Office for Radiation Protection (number Z5-22461-2-2011-002). It was conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki. After complete description of the study to the participants, written informed consent was obtained.

3. Measures

3.1. Three-Factor Eating Questionnaire

We applied the German version of the Three-Factor Eating Questionnaire (Pudel & Westenhöfer, 1989). It is a well-established 51-item self-report questionnaire for the assessment of three constructs: cognitive restraint (21 items), disinhibition (16 items) and hunger (14 items). Responses are scored 0 or 1 and summed; herein higher scores denote higher levels of the respective construct. This measure demonstrates adequate internal consistency (Cronbach's alpha ranging from 0.79 to 0.92), and good convergent and discriminant validity (Allison, Kalinsky, & Gorman, 1992). Further, a study investigating a community-recruited sample of overweight individuals (N = 201) and obese individuals (N = 101) and normal weight matched controls concluded that self-report eating disorder measures (including the TFEQ) are valid and reliable among weight groups (Bohrer, Forbush, & Hunt, 2015).

4. PET and MR imaging

Detailed methods have been described previously (Hesse et al., 2017). In short, all participants underwent dynamic PET after intravenous bolus injection (90 s) of 359 ± 11 MBq [^{11}C]MRB using the ECAT EXACT HR + scanner in three-dimensional acquisition mode (Siemens, Erlangen, Germany; intrinsic resolution at the centre 4.3 mm full-width at half maximum). Scans were not performed in fasting state. Participants were encouraged to have a light breakfast on the day prior to PET scanning. MRI scans were obtained using a 3T scanner (Magnetom Verio, Siemens, Germany; T1-weighted 3D magnetization prepared rapid gradient echo; time of repetition 2300 ms, time of echo 2.98 ms, 176 slices, field of view 256 × 240 mm, voxel size 1 × 1 × 1 mm). Individual MR data sets were spatially reoriented onto a standard brain data set similar to the Talairach space using the image processing software PMOD version 3.4 (PMOD Technologies Ltd, Zurich, Switzerland). Volumes of interest were drawn by hand on three consecutive transversal slices of the reoriented individual MRI data sets (slice thickness: 2.5 mm). 13 different brain regions were further investigated (frontal cortex right and left (r/l), dorsolateral prefrontal cortex r/l, orbitofrontal cortex r/l, insular cortex r/l, locus coeruleus (LC), thalamus r/l, hypothalamus r/l). The regions were drawn manually by one independent researcher and experienced reader after sufficient training period. Tissue time activity curves (TACs) were obtained from the dynamic PET data using PMOD. Kinetic modeling of these regional brain TACs was performed using the multilinear reference tissue model MRTM2 (2 parameters) (Ichise et al., 2003) with the occipital cortex as reference region (Hannestad et al., 2010) and simultaneously by applying the 2-tissue compartment model of a target region with rate constants and the 1-tissue compartment model of the reference region. Regional NET binding potential (BP_{ND}) values were then calculated (Hesse et al., 2017). SPSS 20 software (SPSS Inc., Chicago, IL, USA) was used to analyze the data. All data are presented as mean and standard deviation, unless otherwise stated. The data were tested for normal distribution using the Shapiro-Wilks test. All our data were normally distributed. Differences in normally distributed data were tested using the Student's *t*-test. Pearson product moment correlation was