Obesity is associated with insufficient behavioral adaptation

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List of abbreviations

ACC	Anterior cingulate cortex
ARC	arcuate nucleus
AgRP	Agouti-related protein
GLP	Glukagon-like peptide
BMI	Body mass index
BOLD	Blood oxygen level-dependent
BP	Binding potential
BP_{ND}	Non-displacable binding potential
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CCK	Cholezystokinin
CNS	Central nervous system
$CRMO_2$	Cerebral metabolic rate of oxygen consumption
DA	Dopamine
DOPA	dihydroxiphenylalanine
dLPFC	Dorsolateral prefrontal cortex
EPI	Echo-planar imaging
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutric acid
GLM	General Linear Model
GLP-1	Glucagon-like peptide 1
GPi	Globus pallidus interna
HD	Huntington's disease
HF	High frequency
HR	Hemodynamic response
IGT	Iowa Gambling Task
L-DOPA	L-3,4-Dihydroxyphenylalanin
LHA	Lateral hypothalamic area
lPFC	Lateral prefrontal cortex
MC4R	Melanocortin receptor 4
MNI	Montreal Neurological Institute

α-MSH	α-melanocyte stimulating hormone
MRI	Magnetic resonanz imaging
NAc	Nucleus accumbens
NPY	Neuropeptide Y
NTS	nucleus of the solitary tract
OFC	Orbitofrontal cortex
PD	Parkinson's disease
PE	Prediction error
PET	Positron Emission tomography
PFC	Prefrontal cortex
PPI	Psycho-physiological interaction
POMC	Pro-opiomelanocortin
RAC	Raclopride
SNpc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
SPM	Statistical parametric mapping
STN	Subthalamic nucleus
TE	Echo time
TR	Repetition time
VBM	Voxel-based morphometry
VMH	Ventromedial hypothalamus
VTA	Ventral tegmental area
WHO	World Health Organisation
WPT	Weather Prediction Task

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1 Introduction

1.1 Obesity - a world wide epidemic

Obesity is defined as an excess bodyfat accumulation. According to the World Health Organisation (WHO) a person is considered overweight with a body mass index (BMI) ≥ 25 kg/m^2 < 30 kg/m^2 and obese with a BMI ≥ 30 kg/m^2. Between 1980 and 2008 the worldwide prevalence of obesity has nearly doubled ([189], figure 1). It is known that obesity is associated with adverse effects on health as heightened blood pressure, increased cholesterol and triglycerides levels, and insulin resistance. With steadily increasing BMI, the risk of coronary heart disease, ischaemic stroke, type 2 diabetes mellitus and several cancer types rise [190]. Every year being overweight or obese causes around 3 million people to die [189]. Taken together, this emphasizes the need for a thorough understanding of possible underlying mechanisms associated with the development of obesity and the implementation of effective prevention and intervention programs to curb the obesity epidemic.

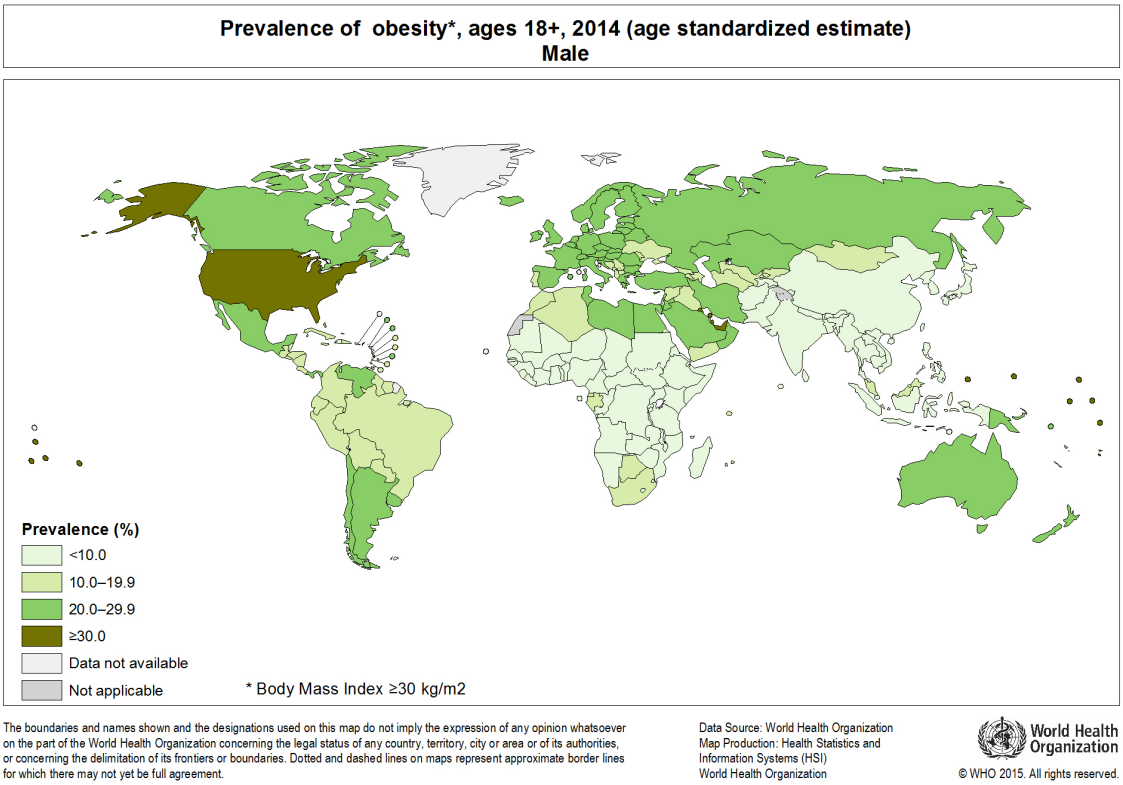

Figure 1:
Obesity prevalence among male adults (2014). Copyright: WHO.

The etiology of obesity is characterized by a complex interplay of numerous interrelated factors. The fundamental cause of excess weight is an imbalance between energy expendi-

ture and intake. Over the last decades, changes in lifestyle and food supply have shaped a so-called 'obesogenic' environment. Increasing motorisation, urbanisation and computerisation have led to a sedentary lifestyle with reduced energy demands. In parallel, the modern food industry is producing more processed, energy-dense and affordable food that is highly advertised and easily accessible [26, 31, 171]. This has led to a general increase in the population's BMI from the early 70s on [148]. Besides these environmental factors, different neurobiological mechanisms explain interindividual differences in weight status and susceptibility to future weight gain. Among them, several genetic loci expressed within the central nervous system (CNS) have been related to individual variation in BMI [164]. From an evolutionary perspective, our central nervous system was optimized to survive in scarce environments. Brain structures accomplishing sensory processing, motivational behavior and reward-based learning have evolved to forage energy-dense food and consume it when accessible even beyond homeostatic needs to survive during periods of food dearth [16, 4]. The tendency to overeat on highly palatable food still seems to be present in many individuals, leading to excess weight and adverse health consequences. In the absence of food shortage periods in our Western civilization, the tendency to overconsume highly palatable food can be regarded as an insufficient adaptation of behavior to our modern food environment within a substantial part of the population. Yet, the underlying neurobiological mechanisms resulting in this insufficient adaptation are still largely unknown [92, 109]. As discussed in section 1.5, neuronal circuits related to processing of food reward stimuli and generation of appropriate response behavior overlap with pathways associated with the processing of reward, related learning and behavioral adjustment in general, outside of a food-specific context. Therefore, it may be assumed that obesity is associated with an insufficient behavioral adaptation even in a general food-unspecific context. To date, only bariatric surgery results in a substantial and relatively stable long-term weight loss [169]. As an invasive intervention, surgery bares serious health risks and can only be regarded as an ultima ratio intervention [2]. To develop efficient noninvasive intervention strategies, we need to understand the behavioral and neuronal alterations that are associated with excess weight. Following this, there is a need for a thorough investigation of possible deficits in behavioral adaptation in obese individuals.

This thesis comprises three behavioral and two neuroimaging studies probing behavioral adaptation. The first two behavioral studies focus on possible obesity-associated alterations in behavioral adaptation in a food-related and a food-unrelated paradigm. In the third study we establish and validate a computational reinforcement learning model in an implicit learning task to assess behavioral adaptation based on an intrinsic learning signal, so called prediction errors (PEs), that is believed to be computed by dopamine (DA) neurons. With the help of positron emission tomography (PET) imaging, we directly relate PE-related behavioral adaptation to DA transmission within the brain and utilize task data from Parkinson's disease (PD) and Huntington's disease (HD) patients to adress

specific hypothesis regarding the associations between specific alterations in DA transmission and attenuated behavioral adaptation. In the fourth functional magnetic resonance imaging (fMRI) study, we utilize the same implicit learning task and computational model to assess alterations in PE-related behavioral adaptation in obesity. Finally, in the fifth study we assess if costs, in the form of physical effort, lead to differential adaptation of behavior in lean and obese individuals. With this last study, we aim at identifying physical effort as a possible target for developing easily implementable intervention strategies to change every day food choices in obese individuals.

This thesis is structured as follows. Sections 1.2 and 1.3 give a short overview of the two main components of eating behavior, that is homeostatic and hedonic eating [147]. The main neurocircuits that are related to homeostatic and hedonic food-intake are presented and their associations with excess weight is described. This is followed by an introduction of the brain's DAergic pathways (1.5) and their relation to adaptive behavior and obesity. The next section explains the main principles of (f)MRI, a powerful non-invasive tool for analyzing the human brain's structure and function. It includes a brief overview into basic statistical analysis of fMRI data and advanced analysis techniques such as computational modeling and psycho-physiological interaction (PPI) analysis. PET, a neuroimaging technique capable of direct assessment of DAergic transmission in vivo, is delineated subsequently. Next, PD and HD are introduced as disease models for specific alterations within segregated DAergic pathways that are essential for efficient behavioral adaptation. Based on this, the rationale for the experimental work is derived 1.11. The presented experimental work resulted in five publications in international peer-reviewed journals that form the present cumulative dissertation (see chapter 2). With a summary that includes a short outlook on future investigations the dissertation is closed (see chapter 3).

1.2 Homeostatic regulation of food intake

Homeostatic regulation of energy intake relates to physiologic processes that ensure adequate nutrition. The notion that energy homeostasis is maintained via a regulatory mechanism of afferrent signals from the periphery to different brain structures was first conceptualized in 1953 [94]. Decisions about daily energy intake are influenced by diverse variables and strongly differ between and within individuals [152]. Nevertheless, due to the process of energy homeostasis human body weight and body fat content are normally relatively stable over time [45, 18]. The energy homeostasis system matches energy intake to energy expenditure over both short- and long-term periods. Blood circulating signals (nutrients and peptides from the periphery) inform brain structures such as the hypothalamus of available energy stores and nutrition status. Via downstream signaling pathways

within the brain, food intake is adjusted accordingly to maintain energy homeostasis (e.g. [123]).

1.2.1 Neurocircuits involved in homeostatic regulation of food intake

Our understanding of the neurocircuitry that regulates energy homeostasis has rapidly grown over the last decades [124]. The central nervous system integrates signals associated with long-term energy stores (e.g. leptin and insulin, circulating hormones that correlate with body fat mass) and short-term meal-related signals (nutrients and gut-derived satiety signals such as ghrelin, cholecystokinin (CCK) or glucagon-like peptide 1 (GLP-1)) to assure stbaility of body fat stores [68, 178, 177]. These regulatory signals can be separated according to being either orexigenic or anorexigenic in nature. Within the CNS, the hypothalamus has been identified as one of the central hubs to integrate homeostasis related signals. The hypothalamus consists of multiple distinct nuclei responsible for a variety of functions through their secretion of neuroendocrine molecules. Among them are sleep, arousal, hunger, thirst and thermoregulation. One key nucleus for the regulation of food intake is the arcuate nucleus (ARC). Within the ARC, two subpopulations of neurons can be distinguished. Pro-opiomelanocortin expressing neurons (POMC) [47, 74] inhibit food intake and increase energy expenditure, while neurons expressing agouti-related protein (AgRP) and neuropeptide Y (NPY) stimulate appetite. Both cell types are targeted by the hormones leptin and ghrelin, the former being secreted by fat cells and the latter by cells in the gastrointestinal tract. Leptin stimulates activity of POMC neurons and inhibits activity of AgRP neurons in the ARC [34] leading to decreased food intake through release of α-melanocyte stimulating hormone (α-MSH) after binding to melanocortin receptor 4 (MC4R). POMC neurons also modulate food intake via projections to the paraventricular nucleus PVN [33, 8] and the ventromedial hypothalamus (VMH, [195]). Conversely, ghrelin-binding inhibits activity of POMC cells and stimulates activity of AgRP/NPY cells within the ARC causing a greater release of NPY and AgRP, and γ-aminobutric acid (GABA) into downstream neurons of the hypothalamus such as those in the PVN to stimulate feeding. Intra hypothalamic communication is far more complex between ARC and other hypothalamic nuclei. Besides its sensitivity to peptides, it is also modulated via GABAergic and Glutamatergic neuronal input [187]. In addition, POMC neurons within the ARC also project to extra hypothalamic regions within the CNS, such as the nucleus of the solitary tract (NTS) located in the medulla oblongata, to suppress food intake [200]. Notably, the neurotransmitter dopamine also impacts on homeostatic regulation of food intake within the hypothalamus. Both, dopamine producing neurons and dopamine receptors are found in several hypothalamic nuclei [121, 61, 188]. Dopamine seems to have opposing effects on food intake according to its site of release. It acts anorexigenic within the VMH and orexigenic within the lateral hypothalamic area (LHA) [115, 114].

Figure 2 provides a simplified overview of the main signals involved in homeostatic eating regulation within the hypothalamus.

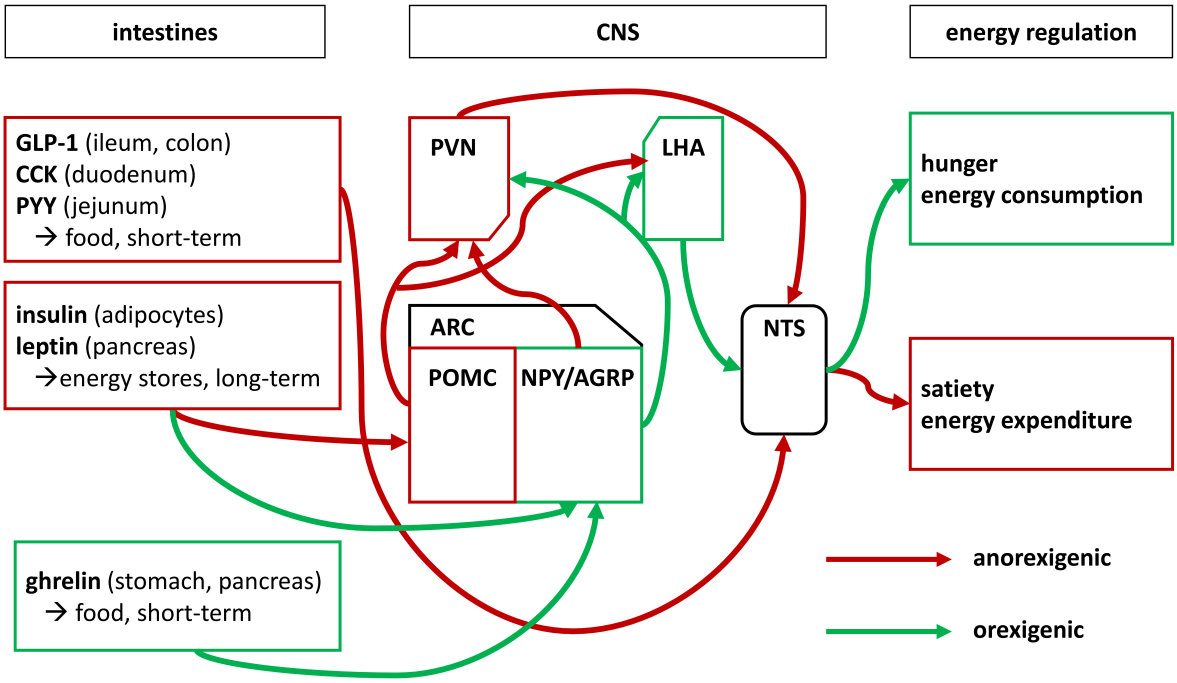

Figure 2:
Schematic representation of the main signaling pathways ivolved in homeostatic food intake control. Within the central nervous system (CNS) hypothalamic nuclei and the nucleus of the solitary tract (NTS) process peripheral orexigenic (ghrelin) and anorexigenic (leptin, insulin, peptide Y (PYY), glucagon-like peptide (GLP-1), cholecystokinin (CCK)) signals. The hypothalamic arcuate nucleus (ARC) can be separated into anorexigenic Pro-opiomelanocortin expressing neurons (POMC) and neurons expressing agouti-related protein (AgRP)and neuropeptide Y (NPY). In response to peripheral stimulation, they either release neuropeptides and neurotransmitters into downstream neurons of the paraventricular nucleus (PVN) and the lateral hypothalamic area (LHA) to induce hunger and initiate energy intake or satiety and energy expenditure. Besides anorexigenic / orexigenic signals from PVN and LHA, the NTS within the brainstem also receives direct anorexigenic signals from the intestines.

1.2.2 Implications for obesity

The main aim of the homeostatic system is the prevention of malnutrition, weight loss and resulting starvation. As leptin is secreted by adipocytes, its plasma level informs the hypothalamus about changes in both energy balance and body fat mass [28, 122]. Decreased leptin signaling provokes increased food intake and higher metabolic efficiency to assure fat accumulation [94, 199, 122]. This has important implications for weight loss attempts in obese individuals as it at least partly explains why people tend to regain weight after dietary interventios [75]. The homeostatic system also prevents against short term weight gain [41, 42, 133], though it is still debated to which extent this holds [102, 101].
Remarkably, the homeostatic system of obese individuals defends body fat stores as

strongly as in lean individuals [157, 42, 102, 143]. One main underlying mechanism might be leptin resistance. Leptin levels are tyically increased in obesity, but its ability to reduce food consumption and body weight is blunted in most obese animals and humans [21, 83, 48, 143]. Several mechanisms may contribute to leptin resistance. Impaired leptin transport across the blood-brain-barrier may be one important cause [24]. Evidence accumulates that excess food intake may lead to neuronal inflammation, gliosis and cell injury within the hypothalamus [195, 39, 87, 172] possibly promoting reduced leptin sensitivity [198]. Notably, recent studies indicate a link between neuronal inflammation and cognitive alterations observed in obesity that may partly be related to inflammation induced disturbances in dopaminergic function within the CNS [25, 138].

1.3 Hedonic modulation of food intake

If food choice and eating behavior were controlled solely by homeostatic mechanisms, the problem of overeating would most likely be neglectable. Yet, consumption of palatable food can be highly rewarding. Hedonic eating refers to the appetitive drive to eat to obtain pleasure in the absence of hunger and can even result in pathological eating behavior [11, 193]. While bland tasting food is typically not consumed to excess, the mere sight or smell of palatable food can trigger food consumption solely due to its rewarding experience and beyond homeostatic needs. From an evolutionary perspective it seems plausible that the inherent pleasurable experience of eating energy dense (highly palatable) food in particular evolved to motivate foraging and consumption of energy dense foods in environments of scarcity [93]. According to Berthoud et al. (2011, [15]), hedonic food intake is a complex process that may be separated into consecutive reward-related phases. Before food is consumed, food reward expectancy plays a key role in whether or not an individual decides to approach and consume available food. To anticipate the rewarding properties of food, dopaminergic neurocircuits within the brain (see section 1.5) use representations of learned food related reward expectations and expected effort requirements from prior experiences to optimize behavior in a neuroeconomic sense [151, 112, 130, 81, 141]. This preparatory phase is followed by the process of food consumption. During consumption, previously acquired reward expectancy is compared with actual reward experience to update future expectations and adapt subsequent food approach behavior accordingly. During food consumption, gustatory and olfactory sensations are primarily responsible for the immediate experience of pleasure until satiation signals dominate [161]. After meal termination the postconsummatory phase starts and lasts until the next meal. It is assumed that nutrient sensing in the gastrointestinal tract also contributes to the experience of reward and with this adds to the reinforcing power of food [153]).
The concept of food reward can be separated into two components, the so called 'liking' and 'wanting' of food reward [11]. Importantly, both are plastic and shaped by predic-

tions formed through learning of respective cue-outcome associations. 'Liking' relates to the hedonic sensation of pleasure experienced during food consumption, whereas 'wanting' characterizes the motivation for obtaining and consuming a respective food reward, also referred to as incentive salience [11]. Incentive salience is attributed to rewards in general and their predictive cues. Thus, 'wanting' of foods can be triggered by food reward predicting cues [194, 135, 54]. 'Wanting' and 'liking' intensity typically correlate for foods, but excessive incentive salience can also drive motivation for obtaining rewarding (food) items that lead to unpleasurable or 'dis-liked' outcomes [173] as proposed for drug addiction, but also obesity [12, 183]. Intense wanting of a particular food (or other potent rewarding substances, such as addictive drugs) is also known as 'craving', a strong desire to purchase and consume the particular substance. Craving severity is associated with BMI and high-caloric snack food [27, 70].

1.3.1 Neurocircuits involved in hedonic eating

Perception of pleasant food stimuli activates multiple neural systems within the brain. Direct sensory feedback from tongue and gut is integrated into basic motor patterns of ingestion already within the caudal brainstem [175, 161]. Cortical areas associated with visual perception and object recognition such as middle occipital gyrus and fusiform gyrus show heightened activation during viewing of food compared with neutral stimuli [179, 88]. Areas within gustatory cortex like operculum and parts of insular are also activated during passively viewing food-pictures [156]. Association and valuation related regions within the fronto-striatal system such as lateral prefrontal cortex (lPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), as well as insular, amygdala and ventral striatum process and integrate food reward related information (olfactory, gustatory, visual and other) to form presentations that guide current and future behavior [15].
In animals, affective studies assessing orofacial expressions as a measure of subconscious pleasentness during tasting foods indicate the existence of several distributed 'liking' hotspots. Among these are the shell subdivision of the NAc and the ventral pallidum [134, 155, 13, 162, 163, 11]. Microinjections of drugs acting on opiod, endocannabinoid or related receptors significantly enhance 'liking' reactions in rodents [134, 108]. Neuroimaging studies in humans indicate that subjective pleasentness ('liking') of food is coded within subdivions of OFC [99]. Anticipation and consumption of palatable food elicits strong activation within reward-related DAergic sides such as NAc and dorsal striatum [159, 160, 165]. Beyond this, activation strength in the NAc to food stimuli seems to be predictive of subsequent food consumption [100]
A (food) reward that was perceived as pleasant in the past is likely to be approached and consumed in the future. This motivational 'wanting' component seems to be powerfully modulated by mesolimbic DAergic signaling [14, 194, 22, 139]. Extending from

the ventral tegmental area (VTA) within the midbrain, DAergic neurons project to the NAc [89] (for further details please see 1.5). Therein, phasic activity of DAergic neurons modulates decision-making processes during the preparatory phase of hedonic eating [23]. Food reward (and other rewards) and their predictive cues trigger mesolimbic DA release [140, 128]. This holds in particular when the perceived reward is unexpected or exceeds our expectations. This is reflected in an increase of the phasic firing rate of DAergic neurons. Whereas, if the (food) reward is lower than expected, DAergic neurons show a transient dip in their background (tonic) firing [151, 119]. In a similar manner, DA transmission also impacts on hedonic food intake during the consummatory phase. DA turnover and transmission rise during consumption of pleasurable foods [159, 46] and short-term consumption of palatable foods even can prime future food intake by strenghtening of synaptic transmission onto DAergic neurons [104]. Importantly, the above described functional characteristics of DAergic transmission within striatum are essential for efficient learning and adequate subsequent behavioral adaptation in general, outside of a food-context. Alterations therein may impact on hedonic eating behavior, but beyond this may also affect learning capabilities and related flexible behavioral adaptation in general.

1.3.2 Implications for obesity

To date, numerous studies have indicated obesity-associated alterations within brain structures involved in hedonic eating. In particular this holds for DAergic pathways within the fronto-striatal system (e.g. [142, 167, 110, 86]). In more detail, obese individuals show greater activation within striatum, ACC, and medial PFC during the presentation of high-caloric food pictures compared with lean subjects [110, 165]. This finding hints at heightened food reward expectation in obese participants that may lead to alterations in food-related stimulus-response learning [129]. In contrast, during consumption of palatable food there is evidence of reduced neural activation within DAergic target regions in striatum [165, 32]. This reduced striatal responsivity to palatable food consumption seems to be at least partly related to prior periods of excess food intake. Women who gained weight over a six month period showed a subsequent reduction in striatal activation during chocolate milkshake consumption [166]. Combining heightened food-reward expectancy and diminished consumatory food reward response strengthens the hypothesis that obese subjects suffer from alterations in food-related stimulus-response learning and associated behavioral adaptation [57]. The mismatch between food reward expectancy and actual reward experience during food consumption does not seem to lead to appropriate downscaling of anticipatory responses and consecutive adaptation of eating behavior in obese individuals.

Although by now there is common agreement on the existence of obesity-related differences

within the DAergic fronto-striatal cirquitry, it is still debated if these differences are (1) cause, (2) consequence or (3) both for the development of obesity (e.g. [15]). While there is evidence for predisposing factors that may increase the risk of future weight gain such as genetic polymorphisms that affect DA receptor density within striatum [165, 38, 50], it seems likely that overeating on highly palatale food leads to functional and structural alterations at least within striatal DAergic target regions [166, 38, 126]. Following up on these findings, Horstmann, Fenske & Hankir (2015) [86] proposed a non-linear relationship between obesity and DAergic transmission in humans. They hypothesize that BMI and striatal DAergic tone are related in an inverted u-shaped fashion and that an altered tonic DA level in obese individuals may be associated with recently observed alterations in executive functioning [52].

1.4 Interaction of homeostatic and hedonic cirquitries

Neurocirquits involved in energy homeostasis and hedonic modulation of food intake interact on several levels [124]. Circulating signals that regulate homeostasis have been shown to modulate DAergic transmission within key regions of the brains mesolimbic DAergic system [51, 125]. The anorexigenic hormones leptin and insulin attenuate DA transmission, increase reuptake of DA into the synapse, and decrease excitability of DAergic neurons [51, 113]. In contrast, the orexigenic peptide ghrelin enhances DAergic function [1]. Besides this interaction on a hormonal/peptide level, both neuronal systems are also interconnected via projecting fibers. NAc sends axons to the LHA. The LHA is assumed to integrate hedonic input related to motivational salience of food stimuli with information of energy homeostasis from ARC [53]. Vice versa, neurons within the LHA project to DA producing cells in the VTA [103] and thus influence DA transmission within NAc. As a result, the perception of highly palatable food can lead to the release of ghrelin in the stomach possibly to some extent via DAergic projections from ventral striatum and thus can alter energy homeostasis [120]. In line with this, decreased leptin levels (e.g. as a result of caloric restriction to loose weight) can lead to overeating partly due to increased rewarding properties of food [64]. This also rises the possibility that changes in circulating hormone levels such as leptin (due to weight gain) may influence behavior that relies on mesolimbic DAergic function even outside of the food context. As obesity has been associated with central leptin resistance, this may lead to alterations in DA transmission within striatum.

1.5 Anatomy & function of the dopaminergic pathways

Besides the involvement in hedonic eating, dopamine (DA) plays a central role in a variety of motivated behaviors (e.g. [144]) and associated learning mechanisms [151, 119] that are crucial for efficient behavioral adaption. DA belongs to the family of catecholamines and functions as a neurotransmitter and neuromodulator within the central nervous system. As DA can not cross the blood-brain barrier it is centrally synthesized from dihydroxyphenylalanine (DOPA). The brain's DAergic system can be separated into three main pathways, the nigrostriatal, the mesolimbic and the mesocortical pathway (see figure 3 for a simplified overview). DAergic input arises from the substantia nigra pars compacta (SNpc) and the VTA. The nigrostriatal pathway originates in the SNpc and projects to the dorsal striatum. It is mainly involved in motor control and the formation of automatic stimulus-response associations necessary for establishing habitual behavior patterns [91]. The mesolimbic pathway sends DAergic input from the VTA to the ventral striatum. From there it is relayed to regions within the limbic system including amygdala, hippocampus, ACC and PFC. It is believed to be the main pathway for reward-related incentive motivation and associated reinforcement learning mechanisms [14, 144, 151]. Direct DAergic projections that arise from the VTA to the frontal lobes are refered to as the mesocortical pathway. Important functions are mediation of behavioral flexibility regarding emotional and motivational aspects in goal-directed behavior [55].
A key role of DAergic transmission is the formation of action-outcome and stimulus–response associations that are essential for the control of motivated behavior by past experience [191]. As a neurotransmitter, DA acts on a short millisecond timescale via phasic release. In contrast, tonic DA transmission acts on a longer timescale of up to several minutes and has modulatory functionality. The phasic DA signal is sensitive to behaviorally salient stimuli and with its fast release properties it is best suited to act as a teaching signal to foster reinforcement learning processes in general reward (e.g. [151, 150]) and food-related contexts [140]. The slower evolving tonic DA transmission is supposed to modulate intrinsic motivation, that is the motivational drive to overcome effort barriers to invigorate behavior [127, 145, 79]. Importantly, the tonic DA signal also interacts with phasic DA release. Background stimulation of DA receptors depends on extracellular tonic DA levels [73]. Furthermore, high tonic DA levels can inhibit the phasic DA response via action on presynaptic D2 auto-receptors [72] or via hyperpolarization of DAergic neurons [44]. Therefore, a balance between tonic and phasic DA transmission might be crucial for efficient functioning.
Whenever our predictions about the outcome of an action prove to be false, we should adjust our respective associations and adapt our subsequent behavior accordingly. This is crucial for efficient and flexible maintenance of goal-directed behavior. Within striatum, DA transmission encodes the difference between our expectations and the actual outcome

[118, 151, 150]. These so-called prediction errors (PEs) represent a teaching signal that is used to update our current beliefs and adjust future behavior accordingly. Positive PEs are signaled via strong increases in the phasic firing rate ('burst'), whereas negative PEs are associated with comparably small reduction in tonic firing ('dip') of DA neurons. DA is assumed to mediate learning from both positive as well as negative PEs, but via two segregated ('direct'/'indirect') pathways within the basal ganlia (comprising striatum and globus pallidus) [60, 59, 58]. In the 'direct pathway', striatal D1 receptor expressing neurons predominantly send inhibitory projections directly to the output nucleus of the basal ganglia, the globus pallidus interna/substantia nigra pars reticulata (GPi/SNr). In the 'indirect pathway' striatal neurons expressing D2-receptors predominantly send inhibitory projections first to the external segment of the globus pallidus [67, 168]. From there inhibitory projections reach the subthalamic nucleus (STN). The STN then sends excitatory projections back to the GPi/SNr. D1-receptors are affine to positive PE-related strong phasic increases in DAergic transmission, whereas D2-receptors are sensitive to detecting small changes in the tonic DA signal that are related to negative PEs. In humans, direct experimental evidence has been provided for this PE model recently [35]. Alterations within these basic DAergic learning mechanisms may induce behavioral changes in various tasks within and outside of the food environment that rely on efficient behavioral adaptation.

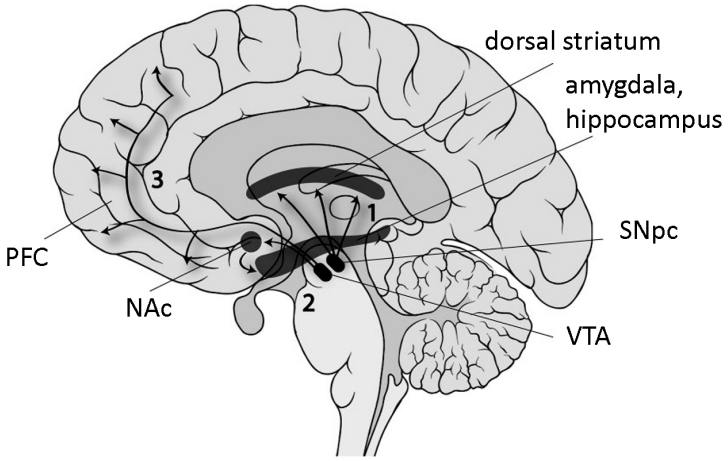

Figure 3:
Schematic representation of the (1) nigrostriatal, (2) mesolimbic and (3) mesocortical DAergic pathways (adapted from [86]).

1.5.1 Implications for obesity

DA signaling within ventral striatum was shown to be implicated in sugar-based flavour conditioning in rodents [154]. To date several studies have assessed associations of BMI and DA receptor availability within striatum in humans [185, 40, 77, 43]. Some of them reported lower striatal DA receptor availability in obese compared with lean subjects

[185, 40], while others found a positive association with BMI [77, 43, 32]. These differences may be related to different BMI ranges of the respective subject samples [86]. According to Horstmann, Fenske & Hankir (2015, [86]) obesity may be associated with an imbalance of phasic and tonic DA release. The authors propose an inverted u-shaped association between tonic DA levels and BMI. Moderately obese individuals may show a reduction in DA tone together with exaggerated phasic DA responses within striatum. In contrast, morbid obesity may be characterized by an increased DAergic tone and associated blunted striatal DA burst firing.
In line with the reported structural differences within the DAergic system, obesity has been associated with functional alterations within the fronto-striatal DAergic pathways. Most of these functional differences have been reported in relation to food reward processing [167, 165]. More recently, research has also focussed on obesity-associated differences in other cognitive domains that relate to alterations in DAeric transmission. Obese individuals performed worse than controls in the Stroop Task [76], a task that tests attentional control. Performance on this task was shown to negatively correlate with tonic DA levels [149]. There is also evidence that behavioral flexibility is reduced in obese compared with lean individuals [17, 182], an important marker of efficient behavioral adaptation capability, modulated by DAergic transmission. Moreover, feedback-related learning may be altered in obesity as well [37, 19]. This may be attributed to an imbalance between phasic and tonic DA regulation in obesity [86]. Altered tonic DA transmission within striatum of obese individuals may impede D2 receptor related modulation of synaptic plasticity during learning and thus may in particular impair behavioral adaptation following negative PEs.

1.6 Magnetic resonance imaging (MRI)

1.6.1 Basic principles of MRI

The following description of the principles of MRI only give a short introduction into the topic. The interested reader may have a look at [20] for a more profound discourse. Nuclear Magnetic Resoncance Imaging ((N)MRI) is an imaging technique that is based on the observation that subatomic nuclei such as protons precess about themselves. This inherent property is called 'spin angular momentum' or 'nuclear spin' in short and is determined by the 'spin quantum number' S. Nuclei with an uneven number of protons (and neutrons) have a non-zero quantum number S. Associated with this intrinsic spin is a magnetic dipole moment $\mu = \gamma S$ that interacts with its electromagnetic environment. Here γ is the gyromagnetic ratio. In the absence of an external magnetic field B_0, the orientation of the magnetic dipole is random. However, if a strong external magnetic field is applied, the magnetic moment aligns with the direction of the external field.

In biological tissue like in the human body, hydrogen nuclei are perfectly suited for MRI. (1) In an external magnetic field hydrogen nuclei have a non-zero spin S as they only consist of one proton. (2) Hydrogen nuclei are highly expressed in the human body. (3) They have a high degree of magnetization (magnetic susceptibility) when located inside a magnetic field.
Hydrogen nuclei can have two possible angular momentum states with respect to the magnitude and orientation of their spin. When placed inside an external magnetic field this relates to two possible different energies that are proportional to the magnitude of B_0. The spins either align in parallel or antiparalell with the external field, relating to a higher or lower energy state. Since the lower energy state has a slightly higher probability this results in a macroscopic longitudinal net magnetization vector M_0 in direction of the external field.
Another important phenomenon utilized in MRI is the observation that the magnetic moment is not static but precesses around the orientation of the external magnetic field with a specific frequency named 'lamor frequency'

$$\omega_0 = -\gamma B_0. \tag{1}$$

Through applying a high-frequency (HF) pulse (excitation) with a frequency close to the lamor frequency ω_0 the spins get in resonance and 'jump' to a higher energy state. This is associated with a tilt of the magnetic vector M_0 of the spins from their original alignment with B_0. The flip angle from their equilibrium orientation depends on the duration of the applied excitation HF pulse. This results in a transversal magnetization component M_{xy} of M_0. In MRI, typically a flip angle of 90° or 180° is applied. After their excitation the protons emit energy in form of electromagnetic waves. This induces a current in a HF receiver coil surrounding the tissue that represents the raw signal in MRI. Relaxation describes the subsequent process of the spins to return to their equilibrium state of realignment to the static field B_0. With it, the emitted signal strength decays exponentially. Relaxation can be separated into a longitudional and a transversal component. Longitudinal relaxation refers to the recovery of the longitudinal component M_z of the net magnetization vector M_0. It is caused by the interaction of the resonating nuclei with their surrounding tissue that absorbs their gained energy from the HF pulse. Thus, it is also called 'spin-lattice relaxation'. The duration for whole recovery of the longitudinal magnetization M_z depends on the 'spin-lattice relaxation time' T1. It ranges between several milliseconds and a few seconds, dependent on the tissue properties. Therefore, it can be utilized to display different tissue types. Transversal relaxation characterizes the process of the transversal magnetization component M_{xy} to decay after the HF pulse. As the spins of the different nuclei interact with each other, they dephase over time. Thus, transversal relaxation is also called 'spin-spin relaxation'. Its duration is characterized by

the time T2. Several other factors as field inhomogeneties of B_0 and the specific susceptibility of the tissue also contribute to the dephasing of the spins and thus to the decay of the transversal component M_{xy}. This is characterized by the time constant $T2^*$.
Often a technical trick is applied to force the spins to precess in phase again. This is achieved by applying a second HF pulse after a time delay τ subsequent to the first HF pulse. This flips the magnetization of the spins by 180° and causes them to precess in phase again after 2τ. With this rephasing of the spins a new transversal magnetization is achieved that is known as 'spin-echo'. When several spin-echos are utilized in a sequence, the related signal decays with the number of 'spin-echos' since not all spins are perfectly rephased (due to spin-spin interactions). The time between excitation and relaxation is called 'echo time' TE.
Excitation and MRI signal readout have to be accomplished with different phase-encoding gradients in a sequence of n steps to achieve a spatial resolution of n lines (e.g. $n = 256$). The signal assessed during all n phase-encoding gradients is stored in a matrix with n rows and is called 'k-space'. With the help of inverse Fourier transformation an image can be reconstructed displaying the spatial distribution of the spin densities (see e.g. [20]).

Typically MRI sequences involve applying a series of HF pulses at a fixed 'repetition time' (TR), to collect sufficient data for adequate image reconstruction. The obtained MRI signal depends on several tissue-specific parameters such as proton density as well as the longitudinal and transversal relaxation times T1 and T2. By adjusting pulse sequence parameters like TE and TR appropriately, the MRI signal can be adjusted to visualize tissue-specific differences such as e.g. differences in 'spin-lattice relaxation time' T1. The resulting MRI signal is called T1-weighted image and T1-weighted sequences are typically added in fMRI studies for exact anatomical localization of the functioal imaging data. FMRI data acquisition itself relies on local differences in the tissue's magnetic susceptibility due to changes in local blood flow (see section 1.6.3) caused by neuronal activation. These local differences cause a faster dephasing of the spins and thus shorter relaxation times, also refered to as $T2^*$-relaxation. FMRI data is normally based on $T2^*$-weighted images.
Since the beginning of the 90's, more sophisticated MRI sequences have been developed for faster image aqcuisition [49]. They take adavantage of the fact that the middle lines of the k-space matrix define the contrast of the image and the outer lines determine the finer details, that is the spatial resolution. For the mid-section, spin-echo sequences are utilized, whereas for the outer lines, so-called gradient-echo sequences are applied. Nowadays, a widely used rapid acquisition sequence is the 'echo-planar imaging' (EPI) sequence. We utilized this technique for functional image acquisition in study 4 (see section **??**). With the help of a sequence of selective gradients, it allows for a readout of the whole k-space

after just one excitation pulse.

1.6.2 Voxel-based morphometry (VBM)

VBM is a neuroimaging approach that allows for an automated investigation of focal differences in brain anatomy. Typically, T1-weighted images are used for VBM-related analysis of brain structure. In a first step, the images are segmented into voxels belonging to grey matter, white matter, or cerebrospinal fluid. Within the statistical parametric mapping (SPM) framework this is achieved via prior probability maps [5]. Subsequent analysis of volumetric differences in local brain structure can be either accomplished in grey- or white matter. In our experimental work (study 2 & 3, see section 2) we were interested in local grey matter volume differences. Raw anatomical images undergo certain processing steps to ensure comparability between subjects for later voxel-wise comparison of grey matter probability values. This includes normalization to a standard brain template, e.g. Montreal Neurological Institute (MNI), usually accomplished via a 12-parameter affine (rigid-body) transformation followed by a nonlinear registration step. This is followed by segmentation of the different tissue types. To correct for volumetric changes introduced by local compression and contraction during normalization, voxel-wise image intensities are modulated (i.e. scaled) according to the normalization parameters [71]. In a final step, the segmented images are smoothed with a Gaussian kernel to increase the validity of parametric testing. Statistical analysis of the smoothed segmented images can be performed with a standard general linear model (GLM) approach 1.6.5.

1.6.3 Blood-oxygen-level-dependent (BOLD) signal & fMRI

Neurons do not have internal energy resources in the form of sugar or oxygen at command. Thus, they have to rely on external supply of both to meet requirements during heightened metabolism. Via a physiological process called 'hemodynamic response' (HR), neuronal activity leads to a proportionate strong local increase in the cerebral blood flow (CBF), a local increase in cerebral blood volume (CBV) and a smaller but significant increase in the local oxygen consumption (cerebral metabolic rate of oxygen consumption ($CRMO_2$) [56, 9, 85]. In sum, this leads to a local decrease in deoxygenated hemoglobin (see Figure 4). Oxygenated hemoglobin is paramagnetic, whereas deoxygenated hemoglobin is diamagnetic. The decrease in deoxygenated hemoglobin content thus leads to a local increase in the ($T2^*$-weighted) MR signal, refered to as the BOLD signal or BOLD contrast. In 2001, Logothetis et al. [106] confirmed that the BOLD-signal more likely reflects neuronal input as assessed by so-called 'local field-potentials', than neuronal output reflected by neuronal spiking activity. Therefore, BOLD contrasts in fMRI studies have to be

interpreted with caution on the neural level, as neuronal input can be of inhibitory or excitatory nature. Following this, fMRI studies can reveal BOLD activation in brain regions that are inhibited and therefore show no activation with single-cell recording techniques [105].

For relieable BOLD contrast images, a large series of T2*-weighted images has to be assessed with a typical TR of around two seconds in between. In a standard fMRI experiment of 30 minutes this would result in 900 whole brain acquisitions. With a typical spatial resolution of 64x64 in xy-direction and 12 slices, each image consists of nearly 50.000 data points (also called 'voxels' - volumetric pixels), resulting in 50.000 time-series of each 900 time points.

During a standard fMRI study, different stimuli (e.g. food pictures on a computer screen) are presented to a subject that are related to a specific task condition (e.g. rating of pictures, memorization, etc.). A trial in an fMRI study is composed of stimulus presentation periods intermingled with resting periods. Each condition consists of a number of similar trials for replication purposes. With this, BOLD activation between specific conditions can be compared or BOLD activation related to a specific condition can be compared with BOLD activation during periods of rest. For a sound statistical analysis of condition-related BOLD activation, trials for each condition should be repeated as often as possible in an at least pseudo-random fashion during a fMRI assessment. To precisely localize the BOLD activation of the different voxels within the brain's anatomy, commonly an anatomical (typically a T1-weighted) image with a heigher resolution (e.g. 256x256 in xy-direction) is obtained additionaly in a fMRI experiment.

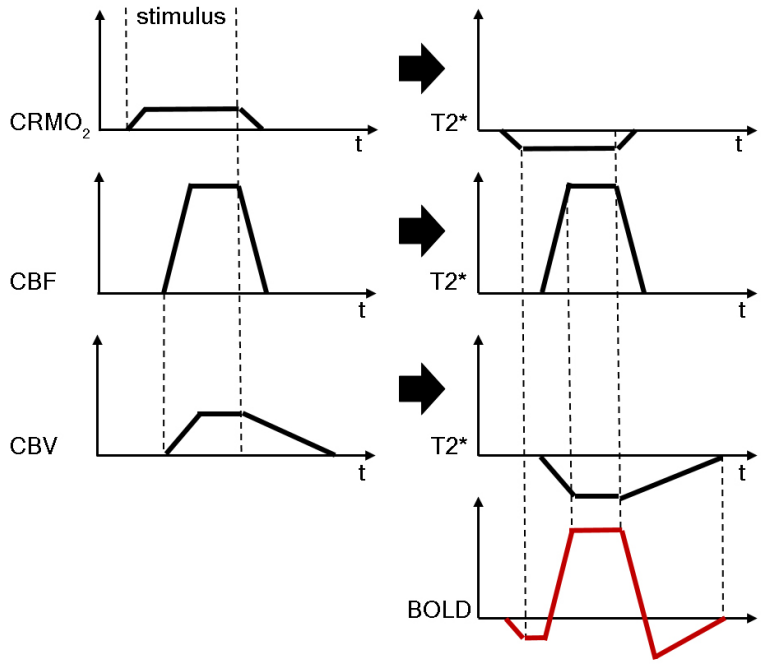

Figure 4:
Schematic representation of the BOLD effect. Stimulus-triggered neuronal activity leads to an increase in cerebral blood flow (CBF) and volume (CBV), and to a smaller increase in oxygen consumption ($CRMO_2$). In sum, this results in a change of the local T2* weighted signal.

1.6.4 Preprocessing of fMRI data

A first important step in analyzing fMRI data is an adequate preprocessing of the raw fMRI signal. Aim of preprocessing is to clean the data from artefacts as e.g. scanner-related low-frequency drifts or subject's head movement during the experiment. A first step in a preprocessing pipeline is the correction of possible head movements of the subject during scanning. Head movements may result in a shift of voxels so that the time courses of single voxels are cut and shifted to other voxels within the brain. With the help of rigid-body transformations the acquired volumes are rotated and shifted to match an a priori selected reference volume (e.g. the first volume). The transformations that lead to the closest match of the volumes are selected as a model for the subject's movement. Another important step is slice-time correction. During each measurement, the single slices are not obtained simultaneously but subsequently with a certain temporal displacement. As in subsequent statistical models, all voxels are treated as if they were assessed simultaneously, interpolation is utilized to correct for this effect. Another possible noise source are low-frequency drifts in the signal that might be of technical (e.g. drift of the external field strength B_0) or of physiological (e.g. fatigue of the subject) nature. With the help of Fourier transformation, the fMRI signal can be transformed from the time into the frequency domain and via applying an appropriate high-pass filter, the low-frequency noise can be removed. Inverse Fourier transformation then results in a new fMRI time

series without low-frequency drifts of no interest. To anatomically localize the BOLD activation within one subject and to statistically infer over brain activation of a group of subjects, the fMRI data has to be aligned with (higher resolution) anatomical data (usually a T1-weighted image) and has to be transferred into a standard coordinate system. Coregistration of the functional to the structural data is achieved via shifting and rotating the functional images and minimizing the statistical difference between them similar to the head motion correction. Normalization on a standard template as the MNI template or the Talairach Atlas can be realized with affine transformations (rotating, shifting, scaling and shearing/skewing) or non-linear transformations (deformation fields).

1.6.5 Statistical analysis of fMRI data

After artefacts in the fMRI signal have been minimized through appropriate preprocessing, the fMRI data can be analyzed. The overall goal of fMRI data analysis is to reveal correlations between the activity of brain regions and the experimental design. The experimental design typically consists of regressors that represent the different experimental conditions. In standard fMRI studies, each single voxel's BOLD activation time series is modeled with the help of the general linear model (GLM) as a linear combination of the effects of the different conditions of interest. This yields:

$$y_k = \sum_{i=0}^{m} x_{ki}\beta_i + \epsilon_k, \quad k = 1, ..., n. \tag{2}$$

In matrix notation this reads

$$Y = X\beta + \epsilon. \tag{3}$$

Here, y_k is the BOLD activation measured at time point k, and x_{ki} represents the value of the ith condition vector x_i at time point k. β_i is the impact strength the ith condition has on the estimation of the BOLD activation as a linear combination of all coditions x_i, $i = 0, ..., m$. The error ϵ_k depicts the difference between the actual BOLD activation and its approximation. The best estimation $\hat{\beta}_i$ of the impact β_i typically minimizes the sum of squares $\sum_k \epsilon_k$ of the error term

$$\hat{\epsilon}_k = y_k - \hat{y}_k, \quad k = 1, ..., n, \tag{4}$$

with

$$\hat{y}_k = \sum_{i=0}^{m} x_{ki}\hat{\beta}_i, \quad k = 1, ..., n \tag{5}$$

being the estimation of y_k. In matrix notation this reads

$$\hat{y} = X\hat{\beta}. \tag{6}$$

The estimation $\hat{\beta}$ can be calculated via computing the generalization of the inverse matrix of X. The $\hat{\beta}_i$ are estimates of the relative BOLD signal change associated with the condition x_i. With these estimates, statistical tests can be performed on the effects of each condition x_i for every single voxel (Friston et al., 1995), e.g. via calculating t-values with

$$t = \frac{c\hat{\beta}}{\sqrt{var(\hat{\beta})}}. \tag{7}$$

Here, the contrast vector $c = c_1, ..., c_m$ determines which conditions should be contrasted. If only the effect $\hat{\beta}_p$ of one condition x_p is of interest, c is one in the p-th entry and zero otherwise. This results in a statistical value for each single voxel. On a whole brain level, this yields a so called 'statistical parametric map' (SPM) of all voxels. The SPM depicts the colour-coded statistical effect (e.g. $F-$, $t-$ or $z-$value) of a condition (or a differential contrast of several conditions) of interest on the BOLD activation throughout the brain. To reveal statistical significant associations, appropriate statistical thresholds have to be applied to the SPMs. This analysis step is conducted on BOLD activation of a single subject. On a next level, the so called second-level analysis, BOLD activation patterns are statistically analyzed on a group of several subjects. With this, BOLD activation related to specific conditions can be generalized on a whole population (given that the sample of participants is sufficiently large) or BOLD activation can be compared between groups of participants, e.g. between healthy controls and patients to draw conclusions on disease-specific alterations in brain function. For a thorough introduction into statistical analysis of fMRI data please see [62].

1.7 Computational modeling & model-based fMRI

A (quantitative) computational model in behavioral or fMRI studies is a mathematical algorithm, e.g. a neural network, that models the 'internal' mapping between a set of task-specific stimuli and a set of behavioral responses. The 'internal/cognitive' operations that effect this mapping are the variables of interest in a computational modeling approach

[131]. These variables can then be subjected to statistical inference, such as comparison between groups of participants (e.g. lean vs. obese), and to regression analysis with the fMRI signal to locate the related processes within the brain of each individual participant. Utilization of computational models in the field of neuroscience grew remarkably since the observation that phasic firing of striatal dopamine neurons (e.g. [151]), as well as the fMRI-related BOLD signal (e.g. [112, 130]), resemble a PE signal used in a variety of mathematical algorithms for reinforcement learning [170]. Thus, in tasks probing learning-related behavioral adaptation, computational modeling is utilized to generate participant specific PE signals as regressors for fMRI analysis and learning-related variables such as learning rates. Within study 3 and 4 (see section 2) we utilized a modified version of a so called 'Q-learning' model (e.g. [58]) to generate subject-specific PEs, as well as learning rates for learning from positive and negative PEs independently. The individual learning rates indicate the strength of positive/negative PE utilization for subsequent behavioral adaptation. In short, a 'Q-learning' model learns to associate a specific response R with an outcome value $Q_t(R)$ at trial t. This expected value is typically initialized to zero and updated in trial $t+1$ via

$$Q_{t+1}(R) = Q_t(R) + \alpha PE_t, \tag{8}$$

where PE_t represents the difference between the expected and actual outcome value in trial t and α depicts the respective learning rate. As human participants do not respond in a deterministic way, their responses are typically modeled to follow a softmax distribution with

$$P_{t+1}(R = j) = \frac{exp(\beta Q_t(R = j))}{\sum_{k=1}^{n} exp(\beta Q_t(R = k))}. \tag{9}$$

Via optimization technigues, the model is fitted to the individual behavior of each subject. With this, one receives participant-specific learning rates α, consistency parameters β, and individual PE signals that can be correlated with the fMRI-related BOLD signal.

1.8 Psycho-physiological interaction (PPI) analysis

FMRI data does not only allow for analyzing task-related brain activation, but also can be utilized to study task-related changes in functional connectivity between separate brain regions. The idea of PPI is that an external 'psychological' variable may interact with the connectivity strength between an a priori selected 'seed' region and other distinct brain regions [63]. For example one may assess if the connectivity strength between primary

visual cortex and other brain regions correlates with strength of task-related attention of the participant. In this example, attention (e.g. on/off) would be the physiological variable. With this approach, task-associated changes in funtional coupling between distinct brain regions can also be compared between separate subject groups, such as lean and obese participants. In study 4, we utilized a PPI analysis approach [132] to test if connectivity strength between ventral striatum and higher cortical areas subsequent to negative PEs is attenuated in obese compared with lean individuals. Here, the presence or absence of a negative PE represents the physiological covariate.

1.9 Positron emission tomography (PET)

1.9.1 Basic principles of PET

PET is a quantitative molecular imaging technique that allows for visualization of neurochemical processes inside the human brain in vivo (e.g. [136]). It relies on positron emission of decaying short-lived radioligands (or radiotracers) that are intravenously administered into the body and bind to molecules of interest within the brain. The radioligand consists of a radioactive nuclide that is incorporated into a biologically active molecule of interest. A positron is an antiparticle of an electron with identical mass but positive charge. After emission, the positron likely collides with an electron in neighbouring tissue. Following the conservation of energy and momentum, it converts its mass into energy and emits two photons of 511 keV each in opposite directions. These two simultaneously emitted 'annihilation photons' form the basis for detection and localization of positron emitting radioligands. Typically, hundreds of so called 'scintillation detector banks' (containing e.g. Bismuth Germinate or Lutetium Oxyorthosilicate) together with photomultiplier tubes are placed in the form of rings surrounding the participant or patient. The detected signals are then fed into separate amplifiers and energy discriminating circuits. The two photons that are emitted in antiparallel direction in an 'annihilation event' hit two detectors in opposite position within the detector rings with only a few nanoseconds time difference at most. This is called a 'coincidence event'. The associated annihilation event can be localized somewhere along the line joining the two detectors. The detection of millions of such coincidence events during PET scanning ensures proper localization and estimation of the concentration of the injected radioligand.

For quantitative assessment of a transmitter system, such as the DA system, PET data has to be acquired dynamically, in contrast to static approaches. This refers to measuring the radioligand's activity within the tissue in a time-dependent manner. Dynamic data acquisition generates so called 'time-activity curves' that depict the concentration of the radioactivity within the tissue (typically Bq/ml) over time. The time-dependent behavior

of the radiotracer is mathematically represented by a set of differential equations. Solutions of these equations yield quantitative outcome parameters, such as 'binding potential' (BP). The most common quantitative measure calculated in dynamic PET imaging approaches is (non-displacable) 'binding potential' BP_{ND}. It is defined as

$$BP_{ND} = f_{ND} B_{max} / KD. \tag{10}$$

Here, B_{max} denotes the total density/concentration of available receptors within the tissue and K_D represents the radioligand equilibrium dissociation constant [117]. The tissue free fraction fND depicts the fraction of radioligand that is freely disolved in tissue water. Proper description of quantitative parameters necessitates information about radioligand concentration within either aterial plasma or brain tissue with negligible few targets (e.g. DA receptors) for the radioligand [196]. For a detailed introduction into the principles of PET scanning see [82, 136].

1.9.2 PET imaging of the DA system

To quantitatively assess the human DA system in vivo, PET imaging with a radioligand that targets the DA system within the brain is utilized. DA can not cross the blood-brain barrier. Therefore, DA specific radioligands can be separated into ligands that either bind to postsynaptic D1-like or D2-like receptors, to presynaptic DA transporters, or to presynaptic enzymes that are involed in DA synthesis. In study 3, we utilized $[^{11}C]$Raclopride (RAC), a common radioligand for binding to postsynaptic D2-receptors. Importantly, for several radioligands such as RAC, BP_{ND} not only assesses the density of the respective receptor within the tissue, but is also an estimate of the extracellular (DA) transmitter concentration. This is due to the fact that the ligand is often displacable by the transmitter itself. Therefore, RAC BP_{ND} can also be utilized to assess DA levels within striatum. In study 3, we employed RAC BP_{ND} to assess tonic DA levels within striatum and phasic DA transmission during implicit learning.

1.9.3 Analysis of PET data

Dynamic PET data necessitates similar preprocessing as fMRI data. For anatomical localization of the acquired data, a high-resolution anatomical MR (e.g. T1-weighted) scan is of great advantage. Utilizing rigid-body transformations, the PET images are anatomically coregistered on the anatomical MR scan. As the radiotracer's distribution and concentration within the brain (in dynamic data acquisition) varies with time, typically

at first only an integrated average (or average over a subsample) of the PET images are coregistered on the MRI scan. Following this, the dynamic images are coregistered to this mean coregisterd PET image. With the help of nonlinear transformations the images are normalized on a standard template (e.g. MNI). This coregistration step also yields appropriate motion correction of the participants in most cases.
For modeling of quantitative parameters such as BP_{ND}, an 'input function' and software implementation of suitable tracer kinetic models are necessary. Input functions provide information about non-specific radioligand uptake. In study 3, we applied a so called 'simplified reference tissue model' with cerebellum as reference region to estimate non-specific uptake. Utilizing nonlinear least-squares estimation or basis function implementations [**?**], parametric maps of quantitative parameters (e.g. BP_{ND}) can be generated. Finally, standard GLM approaches (similar to fMRI data analysis, section 1.6.5) can be applied to model task condition or subject/patient group specific radioligand concentrations.

1.10 Disease models of alterations in the DAergic system

As outlined above (see section 1.5), the DA system within the basal ganglia consists of a direct and indirect pathway. It is assumed that the two pathways play distinct roles in behavioral adaptation subsequent to positive and negative PEs. Within the direct pathway, behavioral adaptation is facilitated via D1-receptor modulated synaptic plasticity following positive PEs, whereas in the indirect pathway, adaptation of behavior is strengthened via D2-receptor modulated synaptic plasticity subsequent to negative PEs [97, 90, 65]. By means of adequate computational modeling (see section 1.7), strength of behavioral adaptation subsequent to positive and negative PEs during learning can be assessed. Specific hypothesis regarding the associations between learning from positive/negative PEs and alterations in DA transmission within the direct/indirect pathway can be tested with the help of patients suffering from diseases that are associated with deteriorations within either one of these segregated pathways. Thus, before we tested our specific hypothesis in study 4 that obese individuals show attenuated behavioral adaptation in particular subsequent to negative PEs, we validated our computational model with task data from Parkinson's disease (PD) and Huntington's disease (HD) patients.
PD is associated with cell death of DA secreting neurons within the SNpc. As stated in section 1.5, these neurons mainly project to the dorsal striatum via the nigrostriatal pathway. As a consequence, DA levels and related activity of DAergic neurons within the dorsal striatum are attenuated. This leads to a heightened inhibition of the motor-system that manifests in hypokinesia, one of the major PD symptoms. To treat this reduction in DA transmission, PD patients are typically treated with the DA precursor levodopa (or L-DOPA) that helps to restore DA levels within striatum. Evidence suggests that in early stages of PD DA depletion is mainly limited to dorsal striatum and the ventral striatum is

relatively less affected [3, 96]. Thus in early PD patients, L-DOPA administration likely leads to excess tonic DA levels within ventral striatum. This may specifically impair learning from negative PEs within the indirect pathway of the basal ganglia [30, 58]. HD is an autosomal-dominant transmitted neurodegenerative disorder caused by a pathologic elongated gene that results from a base triplet elongation on chromosome 4. In early stages of HD mainly the striatum is affected. The progression of neuronal death in the striatum is gradual and proceeds from dorsal to ventral and from medial to lateral [184, 6]. In early stages of HD, cell death primarily affects GABAergic medium-sized spiny neurons within the basal ganglia. This leads to an overactivation of the direct pathway, resulting in the typical early symptoms of the disease, such as hyperkinesias. Therefore, early HD patients may specifically show alterations in learning from positive PEs, due to an overactivation of the direct pathway. In study 3, we assessed PE-related learning in both PD and HD patients to validate a computational model that is capable of capturing behavioral adaptation deficits related to specific alterations within the direct and indirect DAergic pathways.

1.11 Rationale of the experimental work

As outlined above, hedonic food intake (1.3.1) is critically modulated by the mesolimbic and mesocortical DAergic pathways. Further, the CNS circuitries that control hedonic and homeostatic eating behavior intersect within the DAergic system (1.4). Evidence accumulates that obesity may not only be associated with alterations in brain function in the context of food reward anticipation and consumption, but rather obese individuals may show alterations in fronto-striatal DAergic function in general (1.5.1). One key indicator of proper fronto-striatal DAergic integrity is efficient adaptation of behavior in the light of a complex, versatile environment. Adequate DAergic transmission within meso- and corticolimbic circuitries is crucial for the formation and utilization of PEs as an intrinsic teaching signal to update current believes and to optimize our behavior in the future. As a result of the heterogeneous findings of obesity-associated alterations in striatal DA receptor binding potential, we assume that moderately obese ($30 < \text{BMI} = 40$) compared with lean individuals show attenuated striatal tonic DA levels [86]. This is expected to impede basal processes related to efficient feedback utilization and thus may alter flexible adaptation of subsequent behavior. We hypothesize that this does not only hold in a food reward specific context, but may also be apparent in general learning-related tasks that rely on efficient utilization of feedback for subsequent behavioral adaptation. Besides its key role in learning-related behavioral adaptation, mesolimbic DA is also known to modulate motivational drive, that is overcoming effort costs to receive rewards [79]. Thus, we assume that obesity is also associated with alterations in behavioral sensitivity to effort costs. Taking together, we expect that obese individuals show alterations in a broad

range of tasks within as well as outside of the food context that rely on dopaminergic transmission modulated behavioral adaptation. We conducted four studies to test specific hypotheses regarding different aspects of behavioral adaptation in obese compared with lean subjects. To relate alterations in behavioral adaptation to possible changes in DAergic transmission within specific DAergic pathways, we assessed learning-related behavioral adaptation in PD, and HD patients, and in healthy participants inside a PET scanner.

In study 1 we assessed the impact of BMI on behavioral adaptation within a snack food context. Typically, incentive motivation to eat food scales with the homeostatic state. We utilized a selective satiation paradigm, also known as 'devaluation' task, to investigate how changes in incentive motivation for snack food impact on subjects' food approach behavior with increasing BMI. In this study, we only tested male participants, to minimize the impact of social norms regarding food choices on subjects' task performance [180]. We hypothesized that obese compared with lean participants would show attenuated behavioral adaptation in the form of a lower sensitivity to changes in motivational value of snack food items.

Next, we tested if obese subjects also show attenuated behavioral adaptation outside of the food environment. Study 2 consisted of a more abstract learning paradigm, a modified version of the Iowa Gambling Task (IGT, [7]). The paradigm mirrors the trade-off between immediate reward from high-caloric food consumption and negative long-term consequences through weight gain. In each experimental block, participants are free to draw cards from two card decks that either result in gaining or losing points. One card deck is advantagous as it leads to a positive long-term outcome, the other card deck is disadvantagous as it causes a long-term loss. Over time, subjects should learn to adapt their choice behavior to maximize their long-term outcome. We expected obese compared with lean subjects to reveal attenuated behavioral adaptation, possibly as a consequence of a lower sensitivity to negative feedback and long-term negative consequences together with a heightened sensitivity to immediate rewards. Besides behavioral assessment, we applied VBM (see section 1.6.2) to assess obesity-related alterations in gray matter volume in fronto-striatal brain regions in a separate subject sample. For both, the behavioral and structural MRI assessments, we were also interested in the impact of gender as a possible modulating factor [84, 78, 197].

In study 3, we aimed at establishing a computational model (see section 1.7) that is capable of linking alterations in PE-associated behavioral adaptation with changes in DAergic transmission within the direct and indirect pathway of the basal ganglia. Therefore, we assessed implicit learning performance (Weather Prediction Task (WPT), [98]) that relies on PE-related adaptation of behavior in healthy participants inside a PET scanner, in PD patients on versus off levodopa medication, and in early HD disease patients compared to

healthy controls. For all three groups we generated a computational reinforcement learning model to assess PE-related behavioral adaptation. We hypothesized that magnitude of phasic DA transmission (as assessed with PET) during learning is linearly associated with strength of behavioral adaptation from positive PEs. We expected that tonic DA levels in ventral striatum (as assessed with PET) show an inverted u-shaped relation with strength of behavioral adaptation from negative PEs. As PD disease patients on levodopa likely suffer from excess tonic DA levels in ventral striatum, we expected PD patients on versus off medication to be specifically impaired in learning from negative PEs. Since early HD patients show an overactivation of the direct pathway within the basal ganglia, we hypothesized that they are specifically impaired in learning from positive PEs compared to healthy controls.

In study 4, we utilized the computational model from study 3 and the same implicit learning task (WPT) to assess obese compared with lean subjects' capability of using positive and negative PEs to update current stimulus-response associations and adapt subsequent behavior. By means of fMRI in combination with the computational model, we assessed BOLD activation differences in obese compared with lean subjects during learning the task and associated PE processing within their brains. Furthermore, we utilized PPI analysis to investigate if obesity-associated differences in PE utilization are related to differences in functional connectivity in lean compared with obese subjects. We hypothesized that obese subjects show attenuated utilization of negative PEs in particular for adaptation of subsequent behavior, possibly due to attenuated tonic DA levels within striatum.

Finally, in study 5 we assess if manipulating costs, in the form of physical effort, induces differential adapation of behavior in obese compared with lean individuals. More specifically, we tested if cost-benefit decisions related to both food and non-food reward can be differentially altered in obese compared with lean individuals through manipulating physical effort costs necessary to obtain reward items. This might give rise to easily implementable intervention strategies for changing rigid and unhealthy food choice patterns in obese individuals, e.g. via repositioning of food assortments in supermarkets or cafeterias. As effort processing is tightly coupled to ventrostriatal DAergic transmission and fronto-striatal integrity [146, 36, 176] we assumed alterations in cost-benefit decision-making in obese compared with lean participants. We further assessed the impact of several possible modulating factors including gender, chronic stress and body dissatisfaction on participants' cost-benefit choices. Moreover, we utilized VBM (see section 1.6.2) in a subsample of the tested participants to assess obesity-associated differences in local grey matter volume and to reveal grey matter correlates of effort-associated motivation and task-induced food craving.

The following section contains five manuscripts that in detail present studies 1-5. All manuscripts have been published in international peer-reviewed journals.

2 Experimental work

2.1 Publication 1: Horstmann et al., 2015

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Research report

Slave to habit? Obesity is associated with decreased behavioural sensitivity to reward devaluation ☆

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Habitual
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Control of food intake

ABSTRACT

The motivational value of food is lower during satiety compared to fasting. Dynamic changes in motivational value promote food seeking or meal cessation. In obesity this mechanism might be compromised since obese subjects ingest energy beyond homeostatic needs. Thus, lower adaptation of eating behaviour with respect to changes in motivational value might cause food overconsumption in obesity. To test this hypothesis, we implemented a selective satiation procedure to investigate the relationship between obesity and the size of the behavioural devaluation effect in humans. Lean to obese men (mean age 25.9, range 19–30 years; mean BMI 29.1, range 19.2–45.1 kg/m^2) were trained on a free operant paradigm and learned to associate cues with the possibility to win different food rewards by pressing a button. After the initial training phase, one of the rewards was devalued by consumption. Response rates for and wanting of the different rewards were measured *pre* and *post* devaluation. Behavioural sensitivity to reward devaluation, measured as the magnitude of difference between *pre* and *post* responses, was regressed against BMI. Results indicate that (1) higher BMI compared to lower BMI in men led to an attenuated behavioural adjustment to reward devaluation, and (2) the decrease in motivational value was associated with the decrease in response rate between *pre* and *post*. Change in explicitly reported motivational value, however, was not affected by BMI. Thus, we conclude that high BMI in men is associated with lower behavioural adaptation with respect to changes in motivational value of food, possibly resulting in automatic overeating patterns that are hard to control in daily life.

Introduction

The motivational value of food scales with homeostatic state; that is, the incentive value of food is lower when subjects are sated compared to when they are fasted (Stoeckel, Cox, Cook, & Weller, 2007). Dynamic changes in motivational value are thought to contribute to the acute control of eating behaviour, e.g. promoting food seeking or cessation of a meal. In obesity, however, accurate adaptation of eating behaviour in response to acute changes in motivational value might be compromised. Obese subjects have been shown to ingest more energy than is required to meet their current homeostatic needs. Thus, disproportionate adaptation of eating behaviour with respect to changes in motivational value might be a possible cause of food overconsumption in obesity.

Effective adaptation of eating behaviour can only be achieved if action control is actually guided by the current motivational value of an actions' outcome. In general, action control can be described as being either predominantly habitual or goal-directed. According to the dual-system theory, flexible and effective behaviour is determined by the balance between goal-directed and habitual systems (Dickinson, 1985). Habitual and goal-directed action control systems are distinguishable by their varying degree of sensitivity to action outcomes, i.e. motivational value. Goal-directed behaviour is characterized by the actor's awareness of the action outcome and

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the ability to flexibly adapt behaviour to current needs and motivational states (Balleine & Dickinson, 1998). The key feature of this system is its sensitivity to changes in motivational value. In contrast, habits are characterized by the actor's insensitivity to action outcomes; that is, the habitual action will be performed regardless of changes in motivational value of the outcome, triggered by action-associated cues. The balance between these action-control systems is influenced by external factors such as stress (Schwabe & Wolf, 2011), personality traits such as impulsivity (e.g. Chase, 2011; Hogarth, 2012), neurologic and psychiatric disorders such as obsessive–compulsive disorder (Gillan et al., 2011), and addiction (Hogarth, Balleine, Corbit, & Killcross, 2012), with the habitual system dominating in each case.

Here, we hypothesized that obesity is associated with a reduced behavioural sensitivity to changes in motivational value of an outcome, indicating habit-like behavioural control and, consequently, leading to overconsumption of food. A classic experimental paradigm to disentangle goal-directed and habitual behavioural control is the selective satiation procedure (Colwill & Rescorla, 1985), which was initially developed for animal research (Murray & Rudebeck, 2013). This procedure is frequently used to test the behavioural effects of manipulating the motivational value of rewards (e.g. Morewedge, Huh, & Vosgerau, 2010). By allowing animals to consume one of two food rewards to satiety, the value of that food reward is decreased and animals subsequently show less motivation to perform actions that lead to the same food reward (Colwill & Rescorla, 1985). This effect has since become known as a 'devaluation effect'. To test our hypothesis, we implemented a selective satiation procedure to investigate the relationship between obesity and the size of the devaluation effect in humans. Lean, overweight and obese subjects were trained on a free operant paradigm. Subjects learned to associate abstract stimuli with the possibility to win different snack food rewards by pressing a response button. After the initial training phase, one of the rewards was devalued by allowing *ad libitum* access. Subsequently, responses to the abstract stimuli indicating different food rewards were measured again. With successful devaluation provided, the magnitude of difference between responses for the devalued item before and after devaluation should vary positively with the degree of goal-directed action control. Consequently, habitual action control would be characterized by a low reduction in responses after devaluation.

Materials and methods

Subjects

30 male participants (mean age 25.93 years, range 19–30 years; mean BMI 29.06 kg/m^2, range 19.20–45.06 kg/m^2) took part in the experiment. Subjects were screened via telephone calls prior to the experiment to explicitly exclude allergies against one of the snack food items *a priori*. Inclusion criteria were age between 18 and 35 years and BMI between 18.5 and 45 kg/m^2. Exclusion criteria were smoking, current use of medication, diabetes mellitus type I or II, or a history of neurological or psychiatric disorders. For each participant, written informed consent was obtained beforehand and the study was carried out in accordance with the Declaration of Helsinki. Since it has been proposed repeatedly that women are more prone than men to adjusting their food intake according to perceived social norms (e.g. Vartanian, Sokol, Herman, & Polivy, 2013), we restricted our sample to men.

Experimental paradigm and measures

Before the experiment, subjects completed visual analogue scales (VAS), indicating their current level of hunger, satiety, and current wanting of two different sweet (M&Ms, gummi bears) and two different savoury (peanuts, pretzels) snack items. Separate VAS were used to assess hunger and satiety since altered eating behaviour has been shown to decrease the linear relationship between these normally inverse measures (e.g. Halmi & Sunday, 1991). For each subject, the most wanted sweet item and the most wanted savoury item were chosen for the subsequent devaluation experiment, and devaluation was performed using the higher-rated of the two, regardless of taste quality to ensure a high initial response rate. Presentation of stimuli and recording of button presses was implemented using Presentation 14.1 (Neurobehavioral Systems Inc., Albany, CA, USA).

Exclusion criteria

In order to ensure a successful implicit devaluation we excluded some subjects from data analysis. Firstly, we precluded one subject who did not currently want any of the possible devalued foods (VAS scale of wanting the devalued item = 0). Secondly, one subject who ate too much of the devalued food to resemble snacking behaviour (cut-off 881 kcal, which is more than the 95th percentile of the distribution and represents about 40% of the recommended total daily calorie intake) was excluded. Of the remaining subjects, only $n = 2$ rated their favourite savoury item higher than the sweet one and, accordingly, were devalued using a savoury snack item. In order to avoid any biasing effect of taste quality due to this misbalance, we furthermore restricted our analysis to those subjects for whom sweet snack items were devaluated. In total, data obtained from $n = 26$ subjects entered statistical analysis.

The experiment consisted of three phases:

1. Training.
   In an initial training phase, subjects learned the association between two abstract stimuli (fractal images, see Fig. 1), their response rate of a button press, and the possibility to win one of two possible rewards (sweet and savoury item). The training phase was separated into 10 blocks, consisting of five blocks for each sweet and savoury food reward in a randomized order and five breaks of 20 s in between. Each block lasted between 20 and 40 s (uniformly distributed, not apparent to the participant). Within these timespans, each *n*th button press, matching an *a priori* generated, uniformly distributed number *n* within the interval [15 *20*], was rewarded and subjects got visual feedback about their won reward for one second. Thus, a high response rate increased the possibility to win a high quantity of food rewards. After non-rewarded button-presses, subjects received a short neutral feedback (grey dot) for 50 ms. Response rate in button clicks per second was recorded for each of the ten consecutive blocks of the training phase. The association between fractal images and type of reward was counterbalanced between subjects. Subjects received the total rewards won at the end of the first phase and were instructed beforehand to consume all of them immediately.
2. Implicit devaluation.
   Subjects were told that there was a short break in the experiment and they were given *ad libitum* access to a huge quantity of one of the rewards. They were told that these snacks were leftovers from a celebration in the department that day and that they may feel free to help themselves to as much of it as they liked. Subjects watched a film (nature documentary) for 30 minutes and subsequently answered a short (fake) questionnaire about its content. The amount consumed from the reward was quantified in grams without subjects' notice, and energy consumed during the break was calculated in kilocalories (kcal).
3. Devaluation test.
   After implicit devaluation, subjects again completed the VAS regarding their current feelings of hunger, satiety and their momentary wanting of the non-devalued as well as the devalued

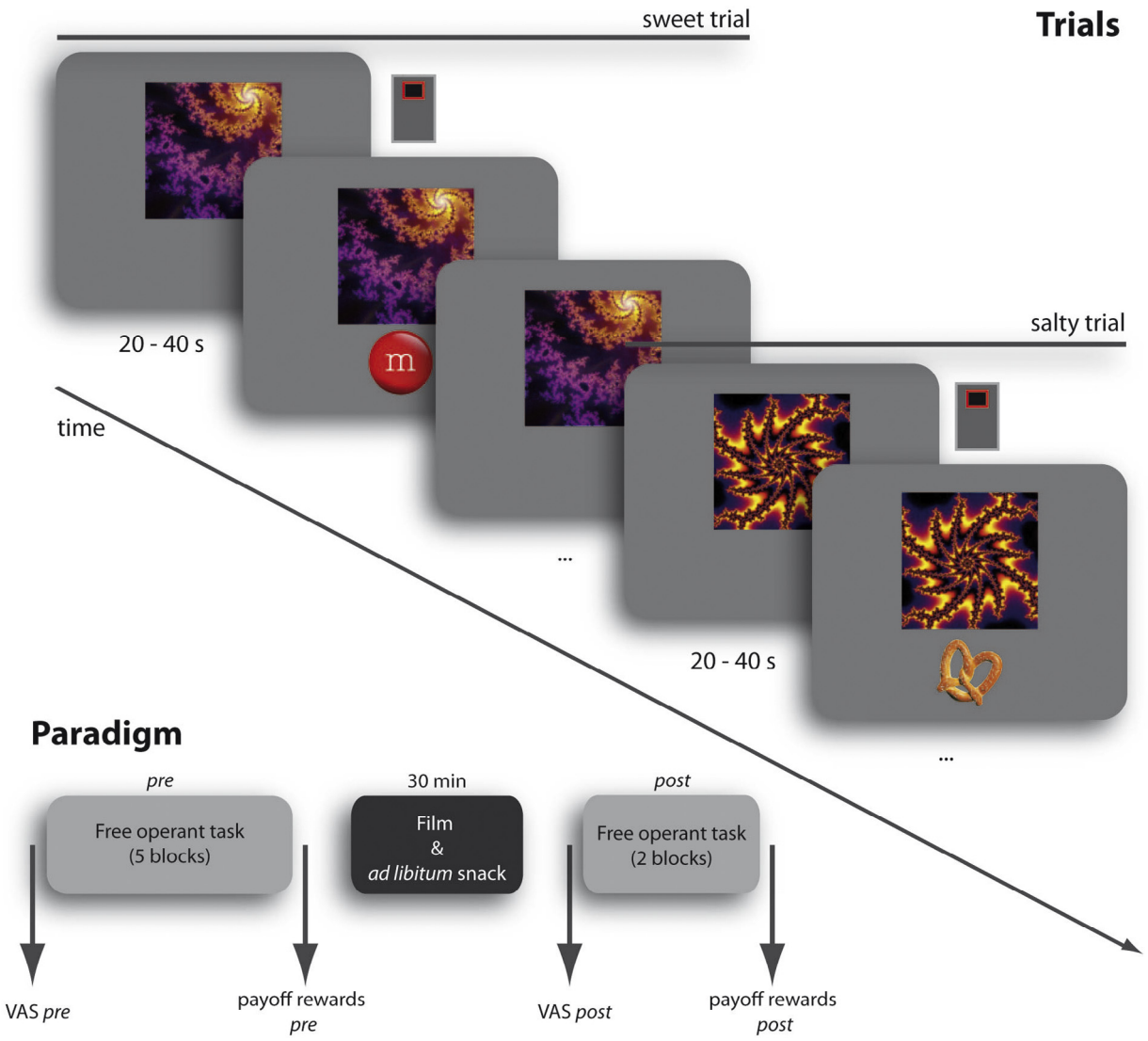

Fig. 1. Trial structure (top) and general experimental paradigm (bottom).

item. Subsequently, response rate to both abstract stimuli was measured again during four consecutive blocks, consisting of two blocks for each reward type in a randomized order with a short break (20 s) in between.

For the calculation of total energy consumed before the test phase, kcals from won items of the training phase were added to the kcals consumed in the devaluation phase.

Questionnaires

We assessed the presence of eating disorders with the help of the Eating Disorder Inventory 2 (Garner, 1991) in order to exclude subjects exhibiting Bulimia Nervosa, Anorexia Nervosa or Binge Eating Disorder. No subjects were excluded because of the presence of eating disorders. To exclude possible confounding effects of depressive symptoms, which may in itself influence drive and motoric vigour, we administered the German version of Beck's Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) with a cut-off value of 18. No subjects had to be excluded because of this criterion.

Statistical analyses

Data were analysed using SPSS software (IBM SPSS Statistics 19.0). Prior to statistical analysis, normality of all data sets was assessed by Kolmogorov–Smirnov tests with no significant results. Therefore, normal distribution can be assumed for all tested variables.

General efficacy of devaluation procedure

To examine the general efficacy of our devaluation procedure, repeated measures ANOVAs were computed on explicit wanting and response rate, using time (pre, post) and reward (devalued, not devalued) as within subject factors, modelling main effects as well as the interaction between both factors. Because we were interested in response rate after initial learning of the contingencies of the task (blocks 1 and 2, see Fig. 2), we averaged the response rate of blocks three to five to represent response rate prior to devaluation (pre-session) and took the average of the two test blocks to represent response rate after devaluation (post-session). Subsequently, planned paired t-tests were used to examine devaluation effects within each reward category separately.

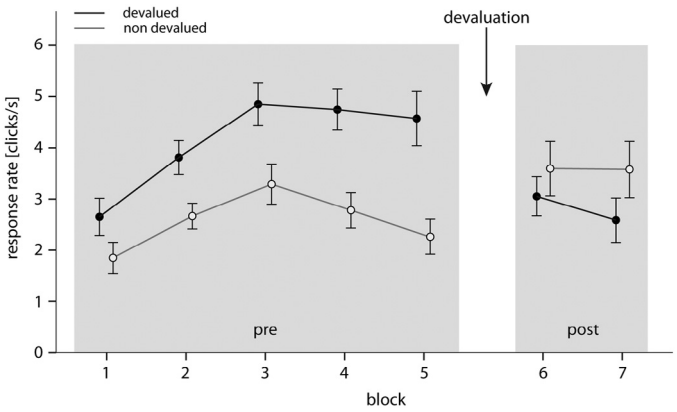

Fig. 2. Evolution of response rates for devalued and not devalued rewards before and after devaluation. Error bars indicate standard error of the mean (SEM); filled circles = responses to devalued reward cue, open circles = responses to non devalued reward cue.

The effect of weight status on devaluation

To examine the influence of weight status on reward devaluation we applied a multiple linear regression analysis. Change in response rate for the devalued item from *pre* to *post* devaluation was the dependent variable and BMI served as predictor variable. Further, we included change in motivational value (i.e. percentage change in current wanting from *pre* to *post*) of the devalued item between pre and post devaluation. In addition, the model was corrected for individual baseline levels of subjective hunger/satiety ratings, presumably reflecting current homeostatic state. Specifically, to avoid influences of multi-collinearity, ratings of satiety prior to the experiment were standardized to the reported levels of initial hunger and both variables were entered in the analysis.

All statistical evaluations were performed at an alpha level of .05.

Results

Participant characteristics regarding age and BMI, along with initial ratings of subjective hunger/satiety prior to devaluation, wanting of devalued item prior to and after devaluation, number of sweet and savoury items won during training, and calories ingested during devaluation are given in Table 1.

There was no significant linear association between total energy intake during the experiment and BMI, reported initial hunger or satiety, or reported initial wanting of the devaluated reward (all $r \leq .318$, *P*-values $\geq .113$). However, there was a moderate positive correlation at trend level between initially reported wanting and subsequent consumption of the devalued reward ($r = .317$, $P = .115$). This indicates that total energy intake may depend on reported initial wanting of the reward, therefore supporting the assumption of ecological validity of the reported VAS values.

Participants learned the association between predictive stimuli, response rate and reward delivery after the two initial blocks of training, as can be derived from Fig. 2, where for both items response rates quickly rise to a maximum after the first two blocks.

First, we investigated the general efficacy of the devaluation procedure on subjectively reported motivational value, i.e. wanting, in the whole sample. A repeated measures ANOVA with the factors time (pre, post devaluation) and reward category (devalued, non-devalued) indicated a significant interaction between time and reward category ($F_{1,25} = 9.09$, $P = .004$) and a main effect of time on explicit wanting ($F_{1,25} = 40.46$, $P < .001$). Next, we analysed specifically whether individual wanting of the devalued item differed between *pre* and *post* devaluation. There was a significant difference, with lower values following devaluation (pre devaluation: mean = 47.12 mm VAS, SD = 26.46; post devaluation: mean = 18.77 mm VAS, SD = 17.99; paired t-test, $T = 6.29$, $P < .001$, Fig. 3A). BMI did not significantly influence the change in individual wanting of either reward type (separate repeated measures ANCOVAS with factor time and BMI as covariate, both *P*-values > .38).

Further, we investigated whether the amount of calories consumed during devaluation significantly influenced the change in reported subjective wanting of the devalued reward before and after devaluation. There was a trend for a direct relationship ($r = -.39$, $P = .052$). This did not change when controlling for participants' BMI via partial correlation ($r = -.384$, $P = .058$); there was still a trend-level negative linear association between the amount of calories consumed during devaluation and the corresponding change in reported wanting, i.e. the more subjects ate during devaluation, the less they explicitly wanted the reward after devaluation.

Second, we analysed whether response rate to the abstract stimulus associated with the devaluated reward dropped in the whole group after devaluation.

Because we were interested in response rate after initial learning of the contingencies of the task, we averaged response rate of blocks three to five to represent response rate prior to devaluation and took the average of the two test blocks to represent response rate after devaluation for the subsequent analysis. A repeated measures ANOVA with within-subject factors time (pre/post) and reward type (devalued/not devalued) showed no significant main effects of either time ($F_{1,25} = 2.41$, $P = .133$) or reward ($F_{1,25} = 3.18$, $P = .087$) on response rate, but a significant interaction of factors time and reward ($F_{1,25} = 9.45$, $P = .005$). Following up on this interaction effect, we performed paired samples t-tests within each condition separately. As expected, there was a decrease in response rate for the devalued food item after devaluation in the whole sample (pre devaluation: mean = 4.72 clicks/s, SD = 1.99; post devaluation: mean = 2.82 clicks/s, SD = 1.97; T-value = 3.11, $P = .005$), but not for the not devalued reward (pre devaluation: mean = 2.78 clicks/s, SD = 1.44; post devaluation: mean = 3.59 clicks/s, SD = 2.70; n.s., Fig. 3B).

Based on our hypothesis we expected an attenuating effect of weight status on the strength of the behavioural devaluation effect. Accordingly, subjects with higher BMI should show a continuing response after devaluation. To examine the link between the strength of devaluation effect and BMI, we applied a multiple linear regression analysis, controlling for initial subjective hunger/satiety ratings and change in wanting of the devalued food item (see Table 1). In Table 2 the statistical association between these variables is given. The model explains 46% of the total variance in behaviour ($F_{(3,25)} = 6.28$, $P = .003$).

Table 1
Participant characteristics.

Male ($n = 23$)	Mean (SD)
Age	25.8 (4.1)
BMI	28.7 (6.72)
Hungry rating *pre* [mm VAS]	27.50 (20.94)
Sated rating *pre* [mm VAS]	61.73 (25.74)
Wanting devalued item *pre* [mm VAS]	47.12 (26.46)
Wanting devalued item *post* [mm VAS]	18.77 (17.99)
Won devalued reward (sweet) [#items] – training session	17.88 (6.64)
Won non-devalued reward (savoury) [#items] – training session	9.50 (4.84)
Energy consumed from devalued reward [kcals] – training session + implicit devaluation	311.09 (223.6)

SD, standard deviation.

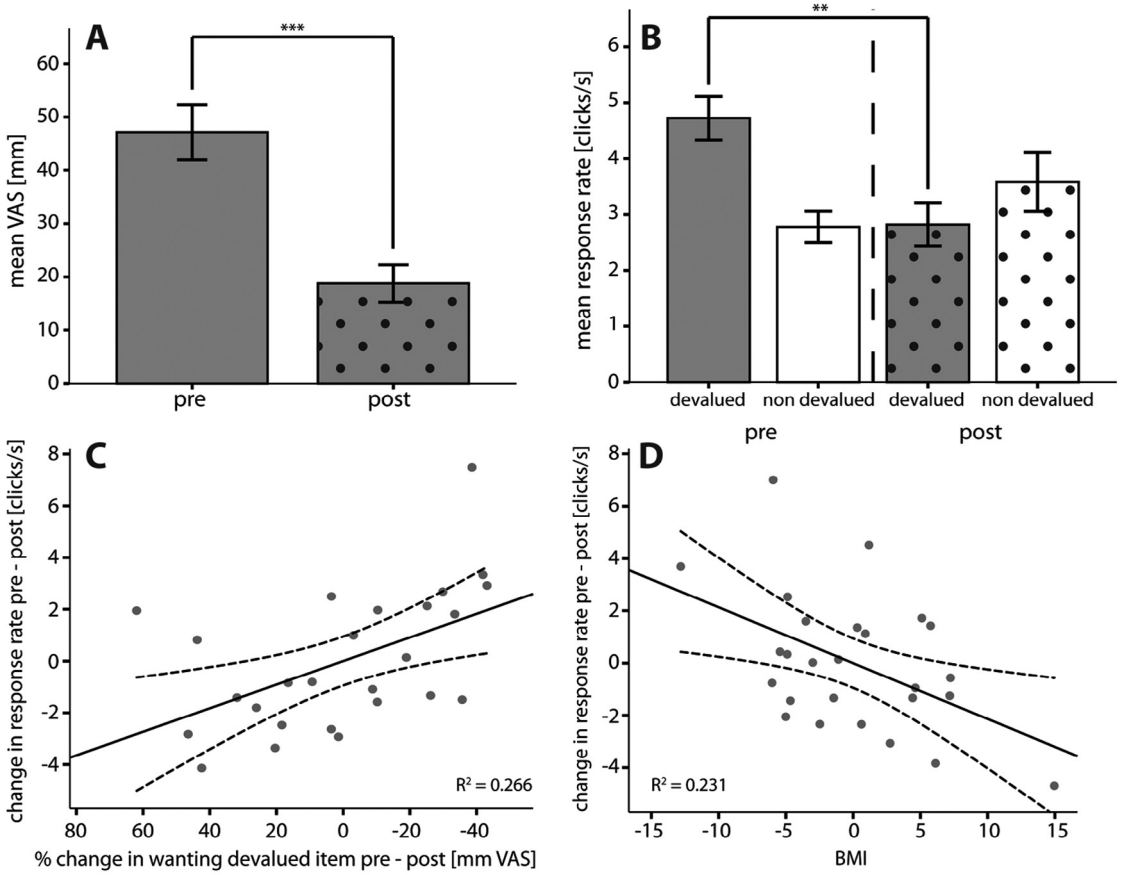

Fig. 3. (A) Significant lower explicit wanting of the devalued reward after devaluation. Error bars indicate standard error of the mean, asterisks indicate *P*-value lower than 0.001. (B) Response rate for devalued and non-devalued prior and past devaluation phase as a measure of success of devaluation. Error bars indicate standard error of the mean, asterisks indicate *P*-value lower than 0.01. (C) Positive relationship between change in reported wanting from pre to post and the change in response rate from pre to post. The positive relationship illustrates that the more subjects' explicit wanting decreased after devaluation, the less vigorous they responded to the devalued reward. (D) Negative relationship between the change in response rate to the devaluated reward and BMI. The negative relationship illustrates that the devaluation effect decreases with increasing BMI. (C) and (D): Partial regression plots, all values are mean standardized for multiple regression analysis and corrected for individual subjective hunger/satiety ratings.

The explicitly reported change in wanting the devalued reward had a significant effect on the magnitude of change in response rate, i.e. the higher the reported decrease in explicit wanting, the higher the decrease in response rate between pre and post (Fig. 3C). Interestingly, BMI had an inverse relationship with decrease in response rate: Higher BMI compared to lower BMI in men led to an attenuated behavioural adjustment to reward devaluation; that is, the difference in response rate before and after devaluation was significantly reduced with increasing BMI (Fig. 3D). Additionally, the induced devaluation effect was found to be greater in subjects reporting higher levels of satiety upon arrival in the lab.

Table 2
Effects of Body Mass Index (BMI), and decrease in motivational value of the devalued food item on the decrease of response rates pre and post devaluation, adjusted for subjects' subjective hunger/satiety rating. Additionally, the influence of initial hunger/satiety rating on the devaluation effect is given.

Variable	Coefficient (standardized)	*t*-Value	*P*-value
BMI	–0.459	–2.57	0.017
Decrease in wanting devalued item [diff mm VAS]	0.449	2.83	0.010
Initial hunger/satiety rating	0.75	3.60	0.002

Discussion

Summary

The current study aimed at examining differences in food-related goal-directed vs. habitual action control associated with weight status. For this purpose a classical devaluation experiment was conducted. First of all we could show that the devaluation procedure was generally successful as explicit wanting ratings and responding for the devalued snack food dropped after the devaluation phase. The change of explicit wanting from pre to post devaluation affected devaluation success, thus emphasizing the role of motivation in goal-directed behaviour. Most importantly, we found a negative relationship between subjects' weight status (i.e. BMI) and the devaluation effect. In accordance with our hypothesis subjects with a high BMI showed an attenuated reduction of responses after the devaluation phase. This indicates lower adaptation to changes in motivational value and corresponding dominance of habit-like behaviour in obesity.

Body weight status and action control

From previous research on sensory-specific satiety it is known that repeated exposure to a certain kind of food leads to a temporary

decline in pleasure derived from consuming that particular food (Havermans, Janssen, Giesen, Roefs, & Jansen, 2009; Rolls, Rolls, Rowe, & Sweeney, 1981; Snoek, Huntjens, Van Gemert, De Graaf, & Weenen, 2004). Further, repeated exposure also leads to corresponding behavioural adaptation, i.e. a decrease in responding for that food due to habituation (reviewed by Epstein, Temple, Roemmich, & Bouton, 2009). It has previously been reported that this behavioural adaptation is slowed down in obesity (Carr & Epstein, 2011; Epstein, Robinson, Roemmich, & Marusewski, 2011). Extending these findings, we showed that induced changes in motivational value after repeated food exposure are not appropriately translated into behaviour in subjects with higher BMI. Further, our study adds the aspect of stimulus-associated responding to the existing literature, allowing interpretation of behaviour in the light of goal-directed vs. habitual action control.

According to the dual-system theory, there are two mechanisms underlying learning and action control (Dickinson, 1985). We assume these mechanisms to account for the observed BMI-related effect on devaluation sensitivity. One mechanism encodes the relationship between actions or responses and their consequences or outcomes (R-O associations), leading to goal-directed behavioural control. A second mechanism is based on the formation of stimulus–response (S-R) associations. These associations are established in proportion to the contingent co-occurrence of the S-R pairs before reinforcement through the outcome. With repetition this leads to stimulus-triggered habitual behavioural control that is independent of outcome retrieval (see Balleine & O'Doherty, 2010, for a review). In general, goal-directed and habitual mechanisms are supposed to be in balance, with one of them predominating according to the particular need, making behaviour flexible (via goal-directed control) and effective (via habitual control) (Dickinson, 1985). Our data support the hypothesis that action control might be shifted towards habitual control in obesity, rendering these two systems unbalanced. Based on the reported relationship between BMI and behavioural devaluation sensitivity we assume dominance of habit-like responding to be a feature of obesity. In accordance with previous studies we presume that there are individuals more sensitive to the rewarding properties of food (Davis & Fox, 2008; Davis, Strachan, & Berkson, 2004; Davis et al., 2007; Franken & Muris, 2005), who regularly overeat on palatable (rewarding) food. A long history of regular excess eating presumably leads to strengthening of S-R, i.e. food cue/consumption associations. As a result eating might change progressively into an automatic or habitual process that is triggered by food stimuli and characterized by reduced sensitivity to changes in motivational value. Unfortunately, we do not have quantitative data on the history of overeating behaviour of our subjects to test this relationship directly in our sample.

Further, in humans, excess weight is related to heightened craving, i.e. the intense desire or urge to eat a specific food (Weingarten & Elston, 1990). Craving-inducing cues are perceived as attractive; they automatically capture attention and trigger appetitive responses that guide behaviour towards target acquisition and consumption. This is called approach bias (Robinson & Berridge, 1993). Interestingly, overweight and obese individuals show an enhanced food approach bias (Havermans, Giesen, Houben, & Jansen, 2011), which is in line with the idea of heightened automatic or habit-like responding for (desired) foods as observed in the current study.

Explicit wanting and action control

The positive relationship between change in wanting from *pre* to *post* and change in response rate from *pre* to *post* indicated that devaluation success was indeed associated with a change in motivation in the present experimental setup. In other words, if there was selective satiation for the devalued item (= low post motivation in comparison to pre motivation), this also translated into behavioural devaluation, thus validating the behavioural paradigm. Motivational value has previously been shown to be an appropriate predictor of food intake in normal-weight subjects: the motivational value (as assessed by explicit wanting) was a better predictor of energy intake than the hedonic value (as assessed by explicit liking) in a non-obese sample (Epstein et al., 2004).

From habits to compulsivity

The current study is to our knowledge the first to investigate the relationship between human body weight status and habitual responding by means of a devaluation experiment. Habitual responding, as observed in the present study, might share characteristics with compulsive behaviour as observed in drug dependence. Typical compulsive actions are mainly cue-triggered. Drug dependency is characterized by such cue-triggered actions (Everitt et al., 2008; Everitt & Robbins, 2005). In obesity, heightened sensitivity to food cues on the behavioural and neural level has been demonstrated repeatedly, indicating higher incentive salience of these cues (e.g. Castellanos et al., 2009; Nijs & Franken, 2012; Nummenmaa et al., 2012). Therefore, overeating patterns in obesity might resemble cue-triggered behavioural patterns of drug-seeking and -taking (Everitt & Robbins, 2005; Volkow, Wang, Tomasi, & Baler, 2013). Previous investigations explored aspects of decision-making behaviour in obesity that may be associated with the gradual development of habits. These investigations demonstrated heightened unpremeditated decision making in obese in contrast to lean individuals (*Delay Discounting Task:* Rasmussen, Lawyer, & Reilly, 2010; Weller, Cook, Avsar, & Cox, 2008; Weygandt et al., 2013; *Stop Signal Task:* Nederkoorn, Braet, Van Eijs, Tanghe, & Jansen, 2006; Nederkoorn, Smulders, Havermans, Roefs, & Jansen, 2006; *Iowa Gambling Task*: Brogan, Hevey, O'Callaghan, Yoder, & O'Shea, 2011; Horstmann et al., 2011; Pignatti et al., 2006; Go/NoGo Task: Batterink, Yokum, & Stice, 2010). Impaired goal-directed control and dominant habit learning have also been associated with trait impulsivity (Hogarth, Chase, & Baess, 2012) in the context of addiction, rendering vulnerable individuals more prone to developing dependency and, consequently, exhibiting compulsive behaviour (Belin, Mar, Dalley, Robbins, & Everitt, 2008; Everitt et al., 2008; Verdejo-García, Lawrence, & Clark, 2008). In rodent studies, it has been demonstrated that drug-naïve high impulsive individuals are more likely to engage in drug self-administration than their low impulsive littermates (Dalley et al., 2007). Interestingly, drug dependency shares several similarities with obesity (García-García et al., 2014; see Volkow et al., 2013, for a review). Thus, a tendency to unpremeditated behaviour might also be a precursor of the transition from goal-directed (reward-driven) to habit-like (stimulus-driven) food consumption. Habitual responding, i.e. behavioural control which is not closely adjusted to current motivational value, may have consequences for both meal initiation and meal termination. In the former case, food intake is initiated without current wanting (i.e. closely related to eating in the absence of hunger); in the latter, a meal is not terminated although the motivational value has already decreased.

Neurobiological basis

The dopaminergic system is prominently involved in reward processing and conditioning of reward-associated stimuli. DA release into the mesolimbic pathway mediates the powerful reinforcing effects of both drugs and food (Small, Jones-Gotman, & Dagher, 2003; Volkow, Wang, Fowler, & Telang, 2008; Volkow et al., 2013). Moreover, DA is also released post-prandially, possibly mediating the successive devaluation of food reward during a meal (de Auraujo et al. Neuron 2008) in addition to its release during anticipation and acute consumption of food rewards. Excessive eating, similar to

chronic drug consumption, progressively leads to alterations in the dopaminergic system, specifically to a down-regulation of striatal dopamine 2 and/or 3 (D2/D3) receptors (De Weijer et al., 2011; Eisenstein et al., 2013; Geiger et al., 2009; Nader et al., 2006; Thanos, Michaelides, Benveniste, Wang, & Volkow, 2007; Wang et al., 2001). This down-regulation, among other factors, is assumed to induce a shift to cue-triggered habit-like consumption (Volkow et al., 2013). Indeed, a recent human PET study reported opposing relationships between striatal D_2-receptor binding potential and opportunistic eating behaviour in ventromedial (negative relationship) and dorsolateral (positive relationship) striatum in obese subjects (Guo, Simmons, Herscovitch, Martin, & Hall, 2014).

On the level of brain structures, the shift from voluntary drug use to compulsive drug-seeking represents a transition from prefrontal cortical to striatal control over drug intake, as well as a switch from ventral (particularly Nc. accumbens) to more dorsal (putamen) domains of the striatum. This shift may at least in part be mediated by the aforementioned gradual changes in dopamine signalling (DA) (Everitt et al., 2008; Everitt & Robbins, 2005; Volkow et al., 2013). With respect to obesity, there are now several studies showing structural as well as functional differences in prefrontal and striatal regions. These differences have been previously associated with variations in reward anticipation and reward processing, as well as behavioural flexibility (e.g. Horstmann et al., 2011; Killgore & Yurgelun-Todd, 2005; Le et al., 2006; Pannacciulli et al., 2006; Rothemund et al., 2007; Stoeckel et al., 2008). Future studies should investigate whether such neuronal alterations are linked to behavioural differences regarding the balance between habitual vs. goal-directed action control in obesity.

Limitations

Due to the finding that women are more likely to adjust food intake according to perceived social norms (e.g. Vartanian et al., 2013), the current study was restricted to males. Therefore, our findings are for now limited to males. Nevertheless, similar mechanisms are expected for women. Upcoming studies should thus especially address this question in women. Additionally, we decided in favour of an implicit devaluation approach as it seemed to be the most natural setting, and subjects were more likely to stay unaware of the fact that the devaluation was part of the experiment. Thus, subjects were not explicitly told to eat one of the food items until it is no longer pleasant to them, but could eat *ad libitum* from the snack to achieve reward-specific devaluation while watching a film. Accordingly, the amount people ate from the reward during devaluation varied between subjects. Future approaches might ensure that subjects ingest a minimum amount of the reward. Further, devaluation efficacy might have been influenced by participants' individual beliefs and expectations about the snack, as well as their eating customs, and the ability to monitor food intake (Higgs, 2008; reviewed by Wansink, 2004). Decisions about food intake, for example, depend on memory of previous food consumption, with the hippocampus playing a crucial role in this context by inhibiting further appetitive responses (Higgs, 2008). Thus, watching the nature documentary in our study might have compromised participants' ability to monitor and memorize food intake by distracting from satiety signals (Bellissimo, Pencharz, Thomas, & Anderson, 2007; Hetherington, Anderson, Norton, & Newson, 2006; Higgs & Woodward, 2009; Temple, Giacomelli, Kent, Roemmich, & Epstein, 2007), leading to decreased devaluation efficacy. Distraction by watching TV could have potentially affected obese participants in particular (Ekelund et al., 2006). Future studies could adapt the procedure in order to avoid potential effects of distractors. Moreover, there was a general preference for the sweet snack across participants. Only few volunteers preferred savoury to sweet snacks and received corresponding devaluation. We initially planned to counterbalance devalued taste qualities between subjects, but for motivational reasons (subjects will respond more for a more wanted snack), we decided to devalue the most wanted snack item. Future studies could screen subjects beforehand to balance the taste quality conditions. Finally, to reduce influences of initial subjective hunger/satiety, it may be advisable in the future to provide a standard breakfast or meal for all subjects before the experiment to ensure a more homogeneous level of hunger and satiety.

Conclusions

To our knowledge, this is the first study that reports differences in food-related goal-directed vs. habitual action control dependent on weight status using a classical devaluation task. We demonstrated that high BMI was associated with heightened habit-like responding for a snack food, i.e. lower adaptation of eating behaviour with respect to changes in motivational value. Importantly, explicitly reported change in motivational value was not affected by BMI.

Regarding daily life, the results of the current study indicate that food intake of particularly overweight and obese men is stimulated by food cues, probably leading to phenomena like eating in the absence of hunger or late meal cessation. Consequently, cue-induced eating may explain an aspect of overweight and obese individuals' difficulties in properly regulating their caloric intake and avoidance of energy overload. Considering that, behavioural sensitivity to devaluation seems to be a useful measure to characterize people's susceptibility to cue-induced overeating.

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Obesity-related differences between women and men in brain structure and goal-directed behavior

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Gender differences in the regulation of body-weight are well documented. Here, we assessed obesity-related influences of gender on brain structure as well as performance in the Iowa Gambling Task. This task requires evaluation of both immediate rewards and long-term outcomes and thus mirrors the trade-off between immediate reward from eating and the long-term effect of overeating on body-weight. In women, but not in men, we show that the preference for salient immediate rewards in the face of negative long-term consequences is higher in obese than in lean subjects. In addition, we report structural differences in the left dorsal striatum (i.e., putamen) and right dorsolateral prefrontal cortex for women only. Functionally, both regions are known to play complimentary roles in habitual and goal-directed control of behavior in motivational contexts. For women as well as men, gray matter volume correlates positively with measures of obesity in regions coding the value and saliency of food (i.e., nucleus accumbens, orbitofrontal cortex) as well as in the hypothalamus (i.e., the brain's central homeostatic center). These differences between lean and obese subjects in hedonic and homeostatic control systems may reflect a bias in eating behavior toward energy-intake exceeding the actual homeostatic demand. Although we cannot infer from our results the etiology of the observed structural differences, our results resemble neural and behavioral differences well known from other forms of addiction, however, with marked differences between women and men. These findings are important for designing gender-appropriate treatments of obesity and possibly its recognition as a form of addiction.

Keywords: gender difference, voxel-based morphometry, obesity, brain structure, Iowa gambling task, reward system

INTRODUCTION

The regulation of body-weight and energy-intake is a complex process involving humoral as well as central homeostatic and hedonic systems. Gender-based differences in the regulation of body-weight covering these domains are reported in the literature. The prevalence of obesity is slightly higher in women (in Germany, where this study was conducted, women 20.2%, men = 17.1%, World Health Organization, 2010) and differences between genders regarding the biological regulation of body-weight have been described for gastrointestinal hormones (Carroll et al., 2007; Beasley et al., 2009; Edelsbrunner et al., 2009) and for eating-related social and environmental factors, as well as for dietary behavior (Rolls et al., 1991; Provencher et al., 2003).

A recent study showed that obesity risk-factors for women and men differ profoundly despite having the same effect on body-weight: for men, most of the difference between groups with high and low health risk was explained by variability in eating competence (a score covering eating attitudes, food acceptance, internal regulation, and contextual skills such as meal planning) and the conscious restriction of food intake. For women, the inability to resist emotional cues and uncontrolled eating explained most of the group-differences (Greene et al., 2011).

These observations hint at fundamental differences in the way women and men process food-related information and control food intake, which is supported by evidence of partly separated neural mechanisms in response to food and in the control of eating behavior for both genders (Parigi et al., 2002; Smeets et al., 2006; Uher et al., 2006; Wang et al., 2009). However, since both men and women can become obese, neither of these ways seems to protect from excess weight gain.

In this study we investigated two aspects of gender-related differences in obesity. First, using voxel-based morphometry (VBM), we assessed differences in brain structure in lean and obese men and women. Second, we explored possible gender-related differences in cognitive control over eating behavior using a modified version of the Iowa Gambling Task (Bechara et al., 1994).

A recent study using functional MRI found gender-related differences in *ad libitum* energy-intake following 6 days of eucaloric feeding as well as in food-related brain activation for normal weight subjects (Cornier et al., 2010). In this study, activation in dorsolateral prefrontal cortex (DLPFC) correlated negatively with energy-intake, but with increased activation levels in women as compared to men. The authors suggested that these greater prefrontal neural

responses in women reflect increased cognitive processing related to executive function, such as guidance or evaluation of eating behavior. In obesity, however, impairment of these control mechanisms may contribute to excess energy-intake.

To investigate possible gender-related differences in cognitive control over eating behavior in obesity, we used a modified version of the IGT. This task requires evaluation of both immediate rewards and long-term outcomes and thus mirrors the trade-off between immediate reward from eating and the long-term influence of overeating on body-weight. Assuming that obese subjects prefer high immediate rewards even in the face of long-term negative outcome, we focused our investigations on card deck B. In this deck high immediate rewards are accompanied by infrequent but high punishments leading to a negative long-term outcome. In order to contrast each of the other decks with deck B individually, we presented only two instead of four alternative card decks at any time. Hypothesizing that obesity differentially affects cognitive control over behavior in men and women, we expected to find effects of both gender and obesity on behavioral measures in the IGT.

Voxel-based morphometry is a valuable tool in identifying differences in the brain's gray matter (GM) structure related not only to diseases but also to task performance (Sluming et al., 2002; Horstmann et al., 2010). Moreover, GM density and structural parameters of white matter have recently been shown to change rapidly in response to altered behavior such as mastering a new skill – in other words, showing that the brain is a plastic organ (Draganski et al., 2004; Scholz et al., 2009; Taubert et al., 2010). Therefore, adaptations in functional circuits due to altered behavior such as persistent overeating could be reflected in the brain's GM structure.

First pioneering studies investigating the structure of the brain in obesity showed obesity-related differences in various brain systems (Pannacciulli et al., 2006, 2007; Taki et al., 2008; Raji et al., 2010; Schäfer et al., 2010; Walther et al., 2010; Stanek et al., 2011) Although being very insightful in identifying brain structures which are different in obesity, those studies did not investigate possible gender-related effects. One study reported an influence of both gender and obesity on the diffusion properties of white matter (Mueller et al., 2011).

We studied the relationship between brain structure and obesity [as measured by body mass index (BMI) as well as leptin] using VBM in both men and women in a normal aged, healthy sample, matched for gender and BMI distribution. Given the above mentioned gender differences in the processing of food-related information, we hypothesized to find gender-dependent in addition to gender-independent correlates of obesity in brain structure.

MATERIALS AND METHODS

SUBJECTS

We included 122 healthy Caucasian subjects. We matched males and females according to distribution and range of BMI as well as age [61 females (premenopausal), BMI (f) = 26.15 kg/m^2 (SD 6.64, 18–44), BMI (m) = 27.24 kg/m^2 (SD 6.13, 19–43), $\chi^2 = 35.66(25)$, $p = 0.077$; age (f) = 25.11 years (SD 4.43, 19–41), age (m) = 25.46 years (SD 4.25, 20–41), $\chi^2 = 11.02(17)$, $p = 0.856$; see **Figure 1** for distribution of BMI and age within both groups]. Inclusion criteria were age between 18 and 45. Exclusion criteria were hypertension, dyslipidemia, metabolic syndrome, depression (Beck's Depression Inventory, cut-off value 18), a history of neuropsychiatric diseases, smoking, diabetes mellitus, conditions which are contraindications to MR-imaging and abnormalities in the T1-weighted MR scan. The study was carried out in accordance with the Declaration of Helsinki and approved by the local ethics committee of the University of Leipzig. All subjects gave written informed consent before taking part in the study.

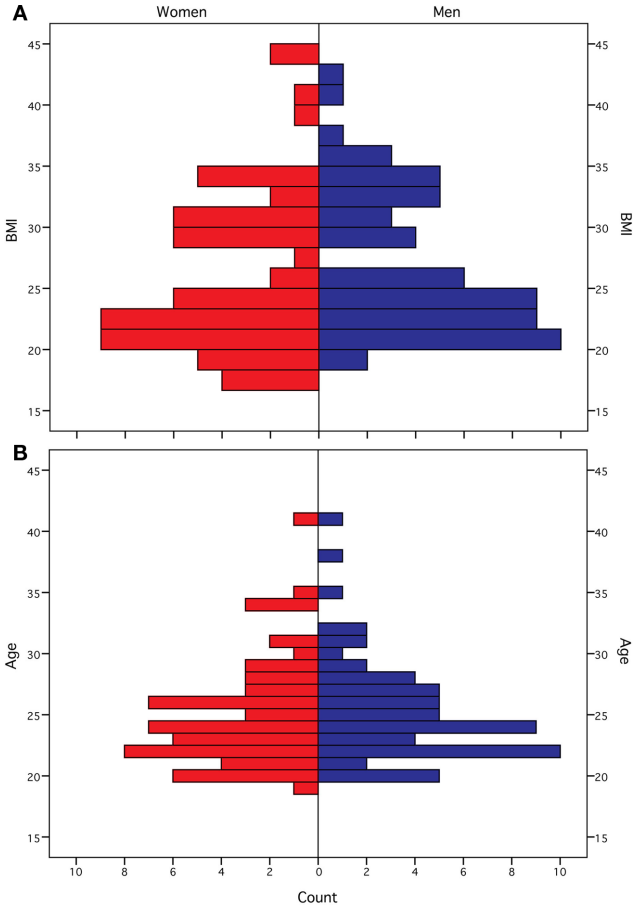

FIGURE 1 | Distribution of body mass index [in kg/m² (A)] and age [in years (B)] for female and male participants.

MRI ACQUISITION

T1-weighted images were acquired on a whole-body 3T TIM Trio scanner (Siemens, Erlangen, Germany) with a 12-channel head-array coil using a MPRAGE sequence [TI = 650 ms; TR = 1300 ms; snapshot FLASH, TRA = 10 ms; TE = 3.93 ms; alpha = 10°; bandwidth = 130 Hz/pixel (i.e., 67 kHz total); image matrix = 256 × 240; FOV = 256 mm × 240 mm; slab thickness = 192 mm; 128 partitions; 95% slice resolution; sagittal orientation; spatial resolution = 1 mm × 1 mm × 1.5 mm; 2 acquisitions].

IMAGE PROCESSING

SPM5 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm) was used for T1-weighted image pre-processing and statistical analysis. MR images were

processed using the DARTEL approach (Ashburner, 2007) with standard parameters for VBM running under MatLab 7.7 (Mathworks, Sherborn, MA, USA). All analyses were performed on bias-corrected, segmented, registered (rigid-body transformation), interpolated isotropic (1.5 mm × 1.5 mm × 1.5 mm), and smoothed (FWHM 8 mm) images. All images were warped based on the transformation of the group-specific DARTEL template to the GM prior image provided by SPM5 to meet the standard stereotactical space of the Montreal Neurological Institute (MNI). GM segments were modulated (i.e., scaled) by the Jacobian determinants of the deformations introduced by normalization to account for local compression and expansion during transformation.

STATISTICAL ANALYSES

The following statistical models were evaluated: a full-factorial design with one factor (gender) and two levels (women and men), including BMI as a covariate centered on the factor mean with no interaction. Additional models included interactions between either BMI or central leptin level and gender to examine the differential effects of these covariates within both groups. All statistical models included covariates for age and total gray and white matter volumes to account for the confounding effects of age and brain size. Results were considered significant at a voxel-wise threshold of $p < 0.001$ with an additional cluster-level threshold of $p < 0.05$ (FWE-corrected, whole brain). Effectively, this combined voxel- and cluster-level statistic reflects the probability that a cluster of a given size, consisting only of voxels with $p < 0.001$, would occur by chance in data of the given smoothness. Results were further corrected for non-isotropic smoothness (Hayasaka et al., 2004).

ANALYTICAL PROCEDURES

Leptin, an adipocyte-derived hormone, is well known to correlate with the percentage of body fat (Considine et al., 1996; Marshall et al., 2000). Central effects for leptin have been extensively described (Fulton et al., 2006; Hommel et al., 2006; Farooqi et al., 2007; Dileone, 2009). We therefore included estimated central leptin level (i.e., the natural logarithm of peripheral leptin, Schwartz et al., 1996) in addition to BMI as measure of obesity. Serum leptin concentration (Enzyme-linked immunosorbent assay, Mediagnost, Reutlingen, Germany) was determined for a subsample [$n = 56$ (24 females), BMI (f) = 27.29 kg/m^2 (SD 6.67, 19–44), BMI (m) = 30.13 (SD 6.28, 20–43); age (f) = 25.33 years (SD 5.27, 19–41), age (m) = 25.19 years (SD 4.5, 20–41)].

MODIFIED IOWA GAMBLING TASK

Participants

Sixty-five healthy participants were tested with the modified Iowa Gambling Task [34 females, 15 lean (mean BMI 21.9 kg/m^2 ± 2.2; mean age 24.1 years ± 2.8) and 19 obese (mean BMI 35.4 kg/m^2 ± 3.9; mean age 25.4 years ± 3.4); 31 males, 16 lean (mean BMI 23.8 kg/m^2 ± 3.2; mean age 25.2 years ± 3.8) and 15 obese (mean BMI 33.5 kg/m^2 ± 2.4; mean age 26.7 years ± 4.0)]. Subjects with a BMI greater than or equal to 30 kg/m^2 were classified as being obese. The four subgroups were matched according to their educational background. One obese female subject was excluded from the analysis due to a thyroid hypofunction.

Experimental procedure

The modified IGT version and behavioral data acquisition were implemented in Presentation 14.1 (Neurobehavioral Systems Inc., Albany, CA, USA). Our modified task version was similar in its general deck composition to the original IGT (Bechara et al., 1994). Decks A and B were disadvantageous, leading to a long-term loss and decks C and D resulted in a positive long-term outcome. Our modifications of the task only pertained to the number of different card decks presented simultaneously and to the gain/loss frequency and gain/loss size in each deck. Participants had to choose between two alternative card decks in each block (e.g., deck B + C). Deck A and C had a gain/loss frequency of 1:1 with an immediate gain of +100 (+70 respectively) and an immediate loss of −150 (−20 respectively). Decks B and D had a gain/loss frequency of 4:1 and yielded immediate rewards of +100 (+50 respectively) and losses in the amount of −525 (−75 respectively). Hence, deck A and B led to an overall net loss while deck C and D led to a net gain.

In every trial, two card decks with a question mark in between were shown on the screen, indicating that subjects had to choose one card. The question mark was replaced by a white cross after participants made their choices. In each trial, participants had to make their decision in less than 3 s. If the subjects failed to select a card within this limit, a smiley with a question mark mouth appeared and the next trial started. These trials were discarded.

Participants completed 90 trials subdivided into 3 randomized blocks (AB/BC/BD) of 30 trials each. After each block, a break of 30 s was introduced, in which subjects were informed that the card decks presented would be different in the following block. Analogously to the original IGT, subjects were told to maximize their outcome via advantageous deck choices.

For motivational issues, participants were paid a bonus of up to 6€ in addition to the baseline payment according to their performance in the task.

Data analysis

All results were computed with PASW Statistics 18.0 (IBM Corporation, Somers, NY, USA). The number of cards drawn from deck B was analyzed with respect to obesity and gender differences including age as a covariate in the general linear model. In addition, learning curves were investigated using a repeated-measures ANOVA. Further ANOVAs to obtain separate group effects for both genders with respect to obesity were performed. The correlation between BMI and preference for deck B was computed using a linear model.

RESULTS

GRAY MATTER STRUCTURE

To explore correlates of obesity in brain structure, we used DARTEL for VBM of the whole brain (Ashburner, 2007) based on T1-weighted MRI. Detailed results are shown in **Figure 2** and **Table 1**. We found a positive correlation between BMI and gray matter volume (GMV) in the medial posterior orbitofrontal cortex (OFC), the nucleus accumbens (NAcc) bilaterally, the hypothalamus, and the left putamen (i.e., dorsal striatum, peak voxels $p < 0.05$, FWE-corrected for multiple comparisons at voxel-level) when both men and women were included in the analysis (see **Figure 2**). Performing the same analysis within the equally sized groups ($n = 61$) of women and

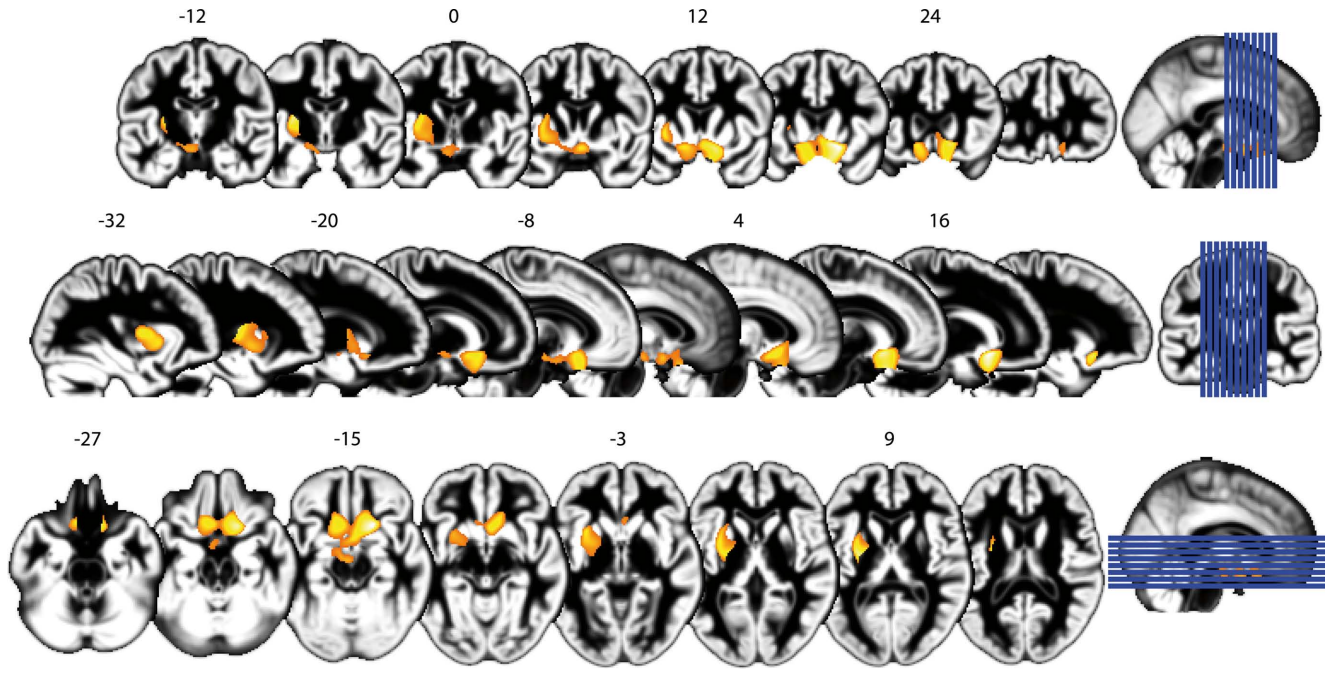

FIGURE 2 | Obesity is associated with structural alterations of the brain's gray matter structure. Results are shown in detail for the whole group (n = 122), including both men and women. Top row: coronal slices, numbers indicate slice location in MNI coordinates. The position of the slices in relation to the whole brain is indicated visually on the right (blue lines). Middle row: sagittal slices, conventions as above. Bottom row: axial slices, conventions as above.

Table 1| Correlations between gray matter and measures of obesity.

GM correlation	Region	Laterality	*x*	*y*	*z*	*z value*	*p*	Sign r
BMI whole group	OFC/NAcc	Left	–10	18	–14	4.41	<0.0001	+
	OFC/NAcc	Right	18	18	–14	5.55	<0.0001	+
	Putamen	Left	–28	–8	10	4.98	<0.0001	+
	Hypothalamus	–	3	6	–15	4.09	<0.0001	+
BMI women	Putamen	Left	–30	–2	10	4.75	<0.0001	+
	OFC/NAcc	Right	21	20	–14	4.28	<0.0001	+
BMI men	OFC/NAcc	Right	14	16	–12	4.15	<0.0001	+
Central leptin women	OFC/NAcc	Left	–16	6	–15	3.76	<0.0001	+
	OFC/NAcc	Right	18	10	–16	3.57	<0.001	+
	Putamen	Left	–22	18	4	4.20	<0.0001	+
	Fornix	–	–2	–4	21	4.07	<0.0001	+
	DLPFC	Right	39	39	32	4.04	<0.0001	–
Central leptin men	OFC/NAcc	Left	–10	3	–12	4.29	<0.0001	+
	OFC/NAcc	Right	9	3	–15	3.90	<0.0001	+
	Hypothalamus	–	2	0	–12	3.54	<0.001	+

Statistical values are given for cluster peaks, coordinates are in Montreal Neurological Institute (MNI) space. GM, gray matter; sign r gives the direction of correlation; OFC, orbitofrontal cortex; NAcc, nucleus accumbens.

men separately, we obtained comparable results for women but not for men: In particular, we found a significant positive correlation between GMV in OFC/NAcc and BMI in both groups (**Figure 3** top row, females $r = 0.48$, $p < 0.001$, males $r = 0.48$, $p < 0.001$) but a significant correlation between the GMV in the putamen and BMI for women only (**Figure 3** middle row, women $r = 0.51$, $p < 0.001$; men $r = 0.003$, $p = 0.979$).

Obese subjects are known to show elevated peripheral leptin-levels, a circulating adipocyte-derived hormone that correlates strongly with the amount of body fat (Marshall et al., 2000; Park et al., 2004). Hence, elevated leptin-levels reflect the amount of excess body fat. As an elevated BMI does not necessarily reflect excess body fat, we used leptin as an additional measure of the degree of obesity to make sure that a high BMI in our sample

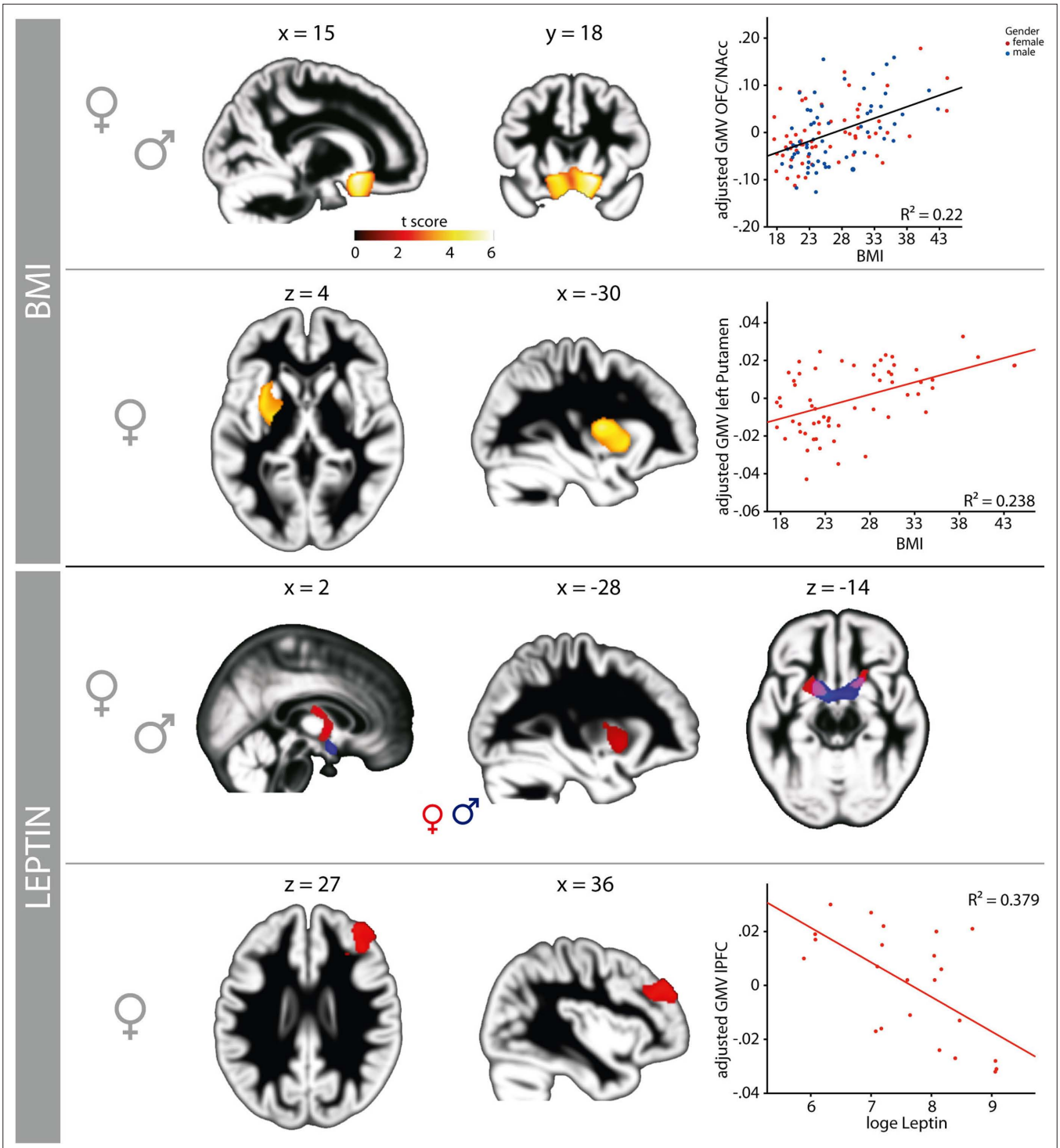

FIGURE 3 | The association of obesity with profound, gender-dependent structural alterations within brain regions involved in reward processing, cognitive, and homeostatic control. The volume of posterior medial orbitofrontal cortex (OFC), nucleus accumbens (NAcc), and hypothalamus increases significantly with BMI (first panel, warm colors) in both genders. For women, an additional association between gray matter volume and BMI can be observed in the left putamen (second panel: warm colors and scatterplot). Leptin, a more direct measure of the degree of obesity, is also associated with gender-dependent changes in brain structure. The association between BMI and GMV in the left putamen overlaps with the association between the concentration of central leptin and GMV in the putamen, an effect, which we only find in women (third panel: red). Women show additional alterations in the NAcc bilaterally and the fornix (third panel, red); men show alterations of brain structure in the NAcc bilaterally and the hypothalamus (third panel, blue). We found a significant negative association between central leptin and GMV restricted to women in the right lateral prefrontal cortex (lower panel). All GMV values are mean standardized and corrected for age, total gray and white matter.

indeed reflects excess body fat rather than excess lean mass. We found that women had a higher absolute serum leptin concentration as compared to men [women 30.92 ng/ml (SD 26.07), men 9.65 ng/ml (SD 8.66), $p < 0.0001$]. An ANCOVA revealed a significant interaction between BMI (2 levels: normal weight ≤ 25; obese ≥ 30), gender, and serum leptin concentration ($F_{1,41} = 16.92$, $p < 0.0001$).

For both men and women, we found a positive correlation between leptin and GMV in the NAcc and ventral striatum bilaterally (women $r = 0.56$, $p = 0.008$; men $r = 0.51$, $p = 0.005$) as well as in the hypothalamus (**Figure 3** third row). Only women show additional leptin-related structural differences in the left putamen and the fornix (**Figure 3**, areas shown in red in third row). The clusters in the NAcc and putamen show a substantial overlap with the regions identified by correlating BMI with GMV (**Figure 3** first to third row). Moreover, only for women did we find an *inverse* (i.e., negative) correlation between leptin-levels and GMV in the right DLPFC ($r = -0.62$, $p < 0.001$; **Figure 3**, bottom row).

RELATIONSHIP BETWEEN GAMBLING BEHAVIOR, GENDER, AND OBESITY

In the IGT, deck B conveys high immediate rewards with each card but low frequency high losses, ultimately resulting in a negative long-term outcome. Hence, the options in deck B mirror the conflict between very salient immediate rewards and the achievement of long-term goals. In the present version of the Iowa Gambling Task, obese women chose significantly more cards from deck B when contrasted with each advantageous deck (i.e., C or D) than lean women across all trials ($F_{1,32} = 8.68$, $p = 0.006$). We found no difference between lean and obese women when contrasting the two disadvantageous decks (i.e., A and B). Additionally, there was a significant correlation between BMI and the total number of cards chosen from deck B for women (**Figure 4A**). Comparing lean with obese men we found neither a significant difference for the total number of cards chosen from deck B ($F_{1,29} = 0.51$, $p = 0.48$), nor a significant correlation with BMI.

In order to test differences in learning behavior between lean and obese participants, we analyzed choices of deck B over time. Over the course of learning, obese women showed no adjustment in choice behavior. In contrast, for lean women we observed a gradual decrease in the preference for cards from deck B (see **Figure 4B**). Thus, obese women did not adapt their behavior toward an overall advantageous outcome compared to lean women. Analysis of learning behavior only revealed a significant effect for obesity in women ($F_{1,30} = 6.61$, $p = 0.015$) but not in men.

This effect of gender was particularly pronounced in the last phase of learning (i.e., trials 25–30), where we observed a significant interaction between gender and obesity for choice behavior on deck B ($F_{1,59} = 6.10$; $p = 0.02$). Here, obese women chose more than twice as many cards from deck B as lean women ($F_{1,33} = 17.97$, $p < 0.0001$). For male subjects, no significant difference was observed (**Figure 4C**, $F_{1,29} = 0.13$, $p = 0.72$). Moreover, a correlation analysis showed a strong correlation ($r = 0.57$, $p < 0.0001$) between BMI and the number of cards chosen from deck B in the last block for women. Again, no significant correlation was observable for men ($r = 0.17$, $p = 0.35$).

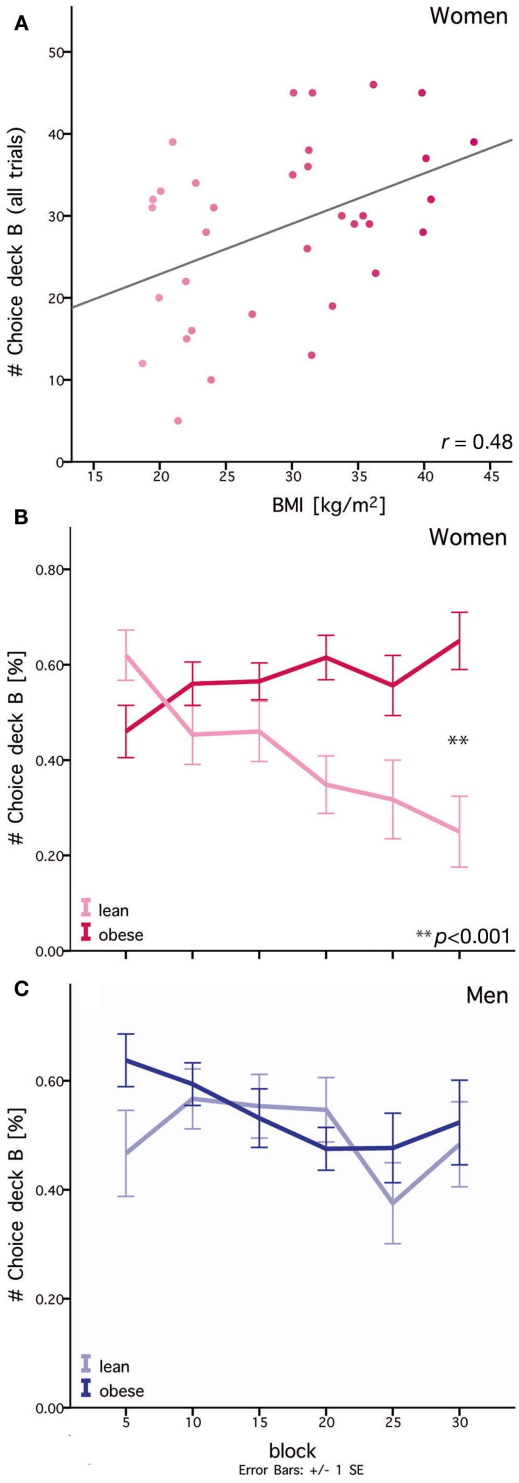

FIGURE 4 | Differences in lean and obese women in their ability to adjust choice behavior to match long-term goals. (A) Preference for deck B over all trials correlates with BMI within the group of women. Gray line: linear regression. **(B)** Difference between lean and obese women in choice behavior during learning. Lean women learn to gradually select fewer cards from deck B. In contrast, obese women continue to select cards from deck B. Each block consists of five trials. **(C)** No difference between lean and obese men in choice behavior is observable during learning. Each block consists of five trials.

DISCUSSION

For both men and women, we show a correlation between GMV and measures of obesity in the posterior medial OFC (mOFC) and within the ventral striatum (i.e., the NAcc) which is in line with previously reported group-differences in GM when comparing lean to obese subjects (Pannacciulli et al., 2006). The interplay between these two regions is crucial for evaluating motivationally salient stimuli (such as food) and relaying this information for the purpose of decision-making. Functionally, these regions code the saliency and subjective value of stimuli (Plassmann et al., 2010). In bulimia nervosa (BN), a condition where eating behavior but NOT BMI differs from normal, GMV of the same structures is higher in patients than in controls (Schäfer et al., 2010). This suggests that the structure of these regions is either affected by or is a predisposition for altered eating behavior instead of being physiologically determined by the percentage of body fat.

In addition to mOFC and NAcc, both genders showed a correlation between brain structure and obesity within the hypothalamus. The hypothalamus is a key region controlling hunger, satiety, eating behavior as well as energy expenditure and possesses direct connections to the reward system (Philpot et al., 2005). We hypothesize that these differences between lean and obese subjects in both the hedonic and homeostatic control systems may reflect one key feature of obesity, namely a bias in eating behavior toward more hedonic food choices where energy-intake exceeds the actual homeostatic demand.

In women only, we additionally show correlations between GMV and measures of obesity (BMI as well as central leptin-levels) in the dorsal striatum (i.e., left putamen) and in the right DLPFC. Interestingly, these structures play important, complimentary roles in habitual (automatic) and goal-directed (cognitive) control of behavior in motivational contexts: The mOFC and NAcc signal the preference for and the expected value of reward, the putamen in the dorsolateral striatum is thought to code (amongst many other functions) behavioral contingencies to obtain a specific reward, and the DLPFC provides goal-directed cognitive control over behavior (Jimura et al., 2010). Goal-directed behavior is characterized by a strong dependency between the likelihood of the response and the anticipated outcome (e.g., Daw et al., 2005). In contrast, habitual (or automatic) behavior is characterized by a strong link between a stimulus (e.g., food) and a response (e.g., its consumption). In this case, the probability of the response is barely influenced by the outcome of the action itself, whether it may be in the short term (satiation) or long-term (obesity).

Recently, Tricomi et al. (2009) investigated the neural basis of the emergence of habitual behavior in humans. They applied a paradigm well known to elicit habit-like behavior in animals, and showed that basal ganglia activations (notably in the dorsal putamen, see also Yin and Knowlton, 2006) increased across training, suggestive of a role in a progressive reinforcement learning process. The functional role of the putamen in this context may be to establish cue-driven sensory-motor loops, and thus to help automate excessively learned behavior. Furthermore, action-outcome representations in the mOFC also continued to increase in anticipation of reward throughout all sessions. These results show that habitual responding does not result from a decrease in the anticipation of reward outcomes across learning, but from strengthening of stimulus-response links (Daw et al., 2005; Frank and Claus, 2006; Frank, 2009). In the context of obesity, Rothemund et al. (2007) previously demonstrated, using an fMRI-paradigm, that BMI predicts activation in the putamen during viewing of high-caloric food in women. Furthermore, Wang et al. (2007) have shown a gender difference in the putamen regarding changes in CBF in response to stress: Stress in women primarily activated the limbic system, including the ventral striatum and putamen.

The basal ganglia are strongly interconnected with the PFC (Alexander et al., 1986), establishing integrative cortico-striato-cortical pathways linking reward-based learning, motivational context and goal-directed behavior (e.g., Draganski et al., 2008). Miller and Cohen (2001) stated that cognitive control over behavior is predominantly provided by the PFC. They conclude that activity in the PFC subserves the selection of a response, which is appropriate in a given situation even in the face of a stronger (e.g., more automatic/habitual or desirable) alternative. It has recently been demonstrated that the DLPFC guides anticipatory implementation of behavioral goals within working memory in rewarding and motivational contexts (Jimura et al., 2010). Gender-related differences for activity in this region in the context of food and control of eating behavior have also been demonstrated recently by Cornier et al. (2010). They found that right DLPFC activation in response to hedonic food was only apparent in women, while men showed a deactivation. Activation in DLPFC was negatively correlated with subsequent *ad libitum* energy-intake, suggesting a specific role of this cortical region in the cognitive control of eating behavior. If one assumes functional relevance of altered brain structure, the negative relationship between GMV in the right DLPFC and obesity found in the present study may be interpreted as an impairment in the ability to adjust current actions to long-term goals or, in other terms, a loss of cognitive control over eating behavior in obese as compared to lean women.

Applying a simplified version of the Iowa Gambling Task, a learning task with very salient immediate rewards conflicting with the achievement of long-term goals, we observed that lean women decreased their choice of deck B over time, while obese women did not. This finding may support the functional relevance of the observed differences in brain structure in rewarding contexts. Differences on the classical IGT between morbidly obese and healthy-weight subjects have been shown recently (Brogan et al., 2011). However, the results of the aforementioned study were not analyzed for influences of gender. Our findings point to a higher sensitivity to immediate rewards in obese than in lean women, accompanied by a possible lack of inhibitory goal-directed control. Further evidence for an impact of obesity on decision-making has been provided by Weller et al. (2008), who found that obese women showed greater delay-discounting than lean women. Interestingly, they did not find differences in delay-discounting behavior between obese and lean men, which corroborates our gender-specific results. Another study, which only included women, tested the impact of obesity on the effectiveness of response inhibition and found that obese women showed less effective response inhibition than lean women in a stop-signal task (Nederkoorn et al., 2006). In the context of eating behavior, less effective behavioral inhibition in combination with a higher sensitivity to immediate rewards may facilitate overeating, especially when faced with a constant supply of highly palatable food.

Koob and Volkow (2010) recently suggested key roles of the striatum, the OFC, and the PFC in the preoccupation/anticipation stage and in disrupted inhibitory control in addiction. They observe that the transition to addiction (i.e., compulsory drug taking) involves neuroplasticity in several central structures and conclude that these neuro-adaptations are a key factor to vulnerability for developing and maintaining addictive behavior. Hence, our findings may support the hypothesis that obesity resembles a form of addiction (Volkow and Wise, 2005), but with marked differences between women and men.

Although we cannot infer functional differences from our findings in brain structure, it is conceivable that the structural differences have also functional relevance. This is further supported by experiments showing modulatory effects of centrally acting gut hormones such as ghrelin, PYY, and leptin on these regions (Batterham et al., 2007; Farooqi et al., 2007; Malik et al., 2008). Dynamic changes in brain structure have recently been shown to parallel learning processes as well as to accompany detrimental progressions such as atrophy (Draganski et al., 2004; Horstmann et al., 2010; Taubert et al., 2010). Since our study, although cross-sectional, included a set of healthy young subjects, we hope to have minimized the possibly confounding effects such as aging and maximized the obesity-specific effects of interest. To our knowledge, we are the first to describe a positive correlation between GM and markers of obesity. The discrepancy between the results published on brain structure and obesity so far and our findings might be explained by differences in sample composition and study design. Studies reporting negative correlations between obesity and brain structure either involved subjects that were considerably older than the subjects in our sample or included subjects with an overall great age range (Taki et al., 2008; Raji et al., 2010; Walther et al., 2010). Detrimental effects of obesity may emerge later in life, so that our findings may describe the early phase of changes in brain structure related to obesity. Also, as these studies were not designed to investigate gender differences, the distribution of genders across lean and obese groups was not explicitly balanced, which may influence the results (Pannacciulli et al., 2006, 2007).

Because our study was cross-sectional, we are not able to make inferences about whether our findings reflect the cause or effect of obesity. It is evenly likely that brain structure predicts the development of obesity or that obesity, accompanied by altered eating behavior, causes brain structure to change. In the future, longitudinal studies may answer this open question.

In summary, we suggest that in both genders, differences of both the hedonic and homeostatic control systems may reflect a bias in eating behavior. Only in women, we show that obesity modulates the behavioral preference for salient immediate rewards in the face of negative long-term consequences. Since behavioral experiments and structural MRI were carried out on different samples (see Materials and Methods) we could not directly relate these behavioral differences to the structural alterations. However, we hypothesize that the additional structural differences seen in obese women can be interpreted as a reflection of behavior paralleling obesity, namely that behavioral control is progressively dominated by habit-like behavior as opposed to goal-directed actions. Furthermore, our findings may be important for the recognition of obesity as a form of addiction. Additional studies of gender differences in behavioral control will be important for investigating the etiology of eating and body-weight disorders and for designing gender-appropriate treatments (Raji et al., 2010).

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The role of dopamine in positive and negative prediction error utilization during incidental learning – Insights from Positron Emission Tomography, Parkinson's disease and Huntington's disease

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ABSTRACT

Incidental learning of appropriate stimulus-response associations is crucial for optimal functioning within our complex environment. Positive and negative prediction errors (PEs) serve as neural teaching signals within distinct ('direct'/'indirect') dopaminergic pathways to update associations and optimize subsequent behavior. Using a computational reinforcement learning model, we assessed learning from positive and negative PEs on a probabilistic task (Weather Prediction Task – WPT) in three populations that allow different inferences on the role of dopamine (DA) signals: (1) Healthy volunteers that repeatedly underwent [^{11}C]raclopride Positron Emission Tomography (PET), allowing for assessment of striatal DA release during learning, (2) Parkinson's disease (PD) patients tested both on and off L-DOPA medication, (3) early Huntington's disease (HD) patients, a disease that is associated with hyper-activation of the 'direct' pathway. Our results show that learning from positive and negative feedback on the WPT is intimately linked to different aspects of dopaminergic transmission. In healthy individuals, the difference in

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PET
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[^{11}C]raclopride binding potential (BP) as a measure for striatal DA release was linearly associated with the positive learning rate. Further, asymmetry between baseline DA tone in the left and right ventral striatum was negatively associated with learning from positive PEs. Female patients with early HD exhibited exaggerated learning rates from positive feedback. In contrast, dopaminergic tone predicted learning from negative feedback, as indicated by an inverted u-shaped association observed with baseline [^{11}C]raclopride BP in healthy controls and the difference between PD patients' learning rate on and off dopaminergic medication. Thus, the ability to learn from positive and negative feedback is a sensitive marker for the integrity of dopaminergic signal transmission in the 'direct' and 'indirect' dopaminergic pathways. The present data are interesting beyond clinical context in that imbalances of dopaminergic signaling have not only been observed for neurological and psychiatric conditions but also been proposed for obesity and adolescence.

1. Introduction

Incidental stimulus-response learning heavily relies on striatal functioning (Jahanshahi et al., 2010; Poldrack et al., 2001). Within the striatum, dopamine (DA) transmission is known to play a key role in fostering learning via encoding the difference between expectations and outcomes of our actions (Montague, Dayan, & Sejnowski, 1996; Schultz, 2002; Schultz, Dayan, & Montague, 1997). These prediction error signals (PEs) are utilized to update current beliefs and, importantly, to adapt subsequent behavior. Positive PEs are signaled via a transient increase in firing rate ('burst') and negative PEs are associated with a pause in tonic firing ('dip'). It has been proposed that DA mediates learning from positive as well as negative outcomes (Van Der Schaaf et al., 2014), but via two segregated ('direct'/'indirect') pathways (Frank, 2005; Frank & O'Reilly, 2006; Frank, Scheres, & Sherman, 2007b; Kravitz et al., 2010). Recently, direct experimental evidence has been provided for this model in healthy volunteers (Cox et al., 2015).

In the 'direct pathway', striatal D1 receptor expressing neurons predominantly send inhibitory projections directly to the output nucleus of the basal ganglia, the globus pallidus interna/substantia nigra pars reticulata (GPi/SNr). Postsynaptic D1 receptors are sensitive to bursts in dopaminergic transmission. Thus, correct stimulus-response associations are strengthened via D1-receptor related modulation of synaptic plasticity within the 'direct' pathway subsequent to positive PEs. In the 'indirect pathway' (Gerfen et al., 1990, pp. 1429–1432; Surmeier, Ding, Day, Wang, & Shen, 2007), striatal neurons expressing D2-receptors predominantly send inhibitory projections first to the external segment of the globus pallidus. From there inhibitory projections reach the subthalamic nucleus (STN). The STN then sends excitatory projections back to the GPi/SNr. 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, too low tonic DA may impair D2 receptor-related signaling, as the magnitude of extracellular tonic DA determines the background stimulation of DA receptors (Grace, 1991). In addition, too high tonic DA release may impede D2 receptor-related signaling, as high tonic DA levels can inhibit the phasic DA response via action on presynaptic D2 auto-receptors (Goto, Otani, & Grace, 2007) or via hyperpolarization of dopaminergic neurons (Dyakonova, Chistopolsky, Dyakonova, Vorontsov, & Sakharov, 2009). Thus, either too low or too high tonic DA levels may specifically impede the capability of detecting dips and, consequently, may alter learning from negative PEs in particular. Further, recent data indicate that the hemispheric asymmetry of DA signals is related to the propensity to learn from positive versus negative PEs (Aberg, Doell, & Schwartz, 2015; Maril, Hassin-Baer, Cohen, & Tomer, 2013; Tomer et al., 2014). A mechanistic explanation for this phenomenon is missing to date.

Consequently, it is important to differentiate between learning from positive and negative feedback to identify the specific involvement of different DA pathways or aspects of DA transmission. Further, an investigation of different aspects of DA transmission based on behavior on the same behavioral task will be beneficial for interpretation of the results.

Here, we assessed learning in response to positive and negative PEs in three populations that allow different inferences on the role of DA in incidental stimulus-response learning. Importantly, all participants completed the same probabilistic learning task, the Weather Prediction Task (WPT, Knowlton, Squire, & Gluck, 1994). To differentiate between learning from positive and negative PEs, we employed a computational reinforcement learning model.

First, we explored the influence of dopaminergic signaling in a sample of healthy volunteers who repeatedly underwent [^{11}C]raclopride Positron Emission Tomography (PET) while completing the WPT with and without corrective feedback. Specifically, we investigated the impact of DA release, tonic DA level, and the asymmetry of phasic responses between left and right striatum on learning from positive and negative feedback. We hypothesized that the strength of phasic striatal DA transmission during procedural learning is linearly related to the participants' capability of learning from positive PEs. Further, we predicted that tonic DA levels within the striatum are associated with the ability to learn from negative PEs in an inverted u-shaped manner. Finally, we expected that asymmetry between left and right striatal signaling is related to learning from positive PEs.

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Second, we investigated the effect of L-DOPA medication on learning from negative PEs in a sample of patients with Parkinson's disease (PD) who were tested both *on* or *off* medication when completing the WPT. Evidence (e.g., Agid et al., 1993; Kish, Shannak, & Hornykiewicz, 1988) suggests that in early PD DA depletion is mainly limited to dorsal striatum and the ventral striatum is relatively less affected. We expected patients *on* levodopa medication to be selectively impaired in learning from negative PEs compared to *off* medication due to an nonspecific increase in dopaminergic tone in the ventral striatum in the *on* state (Cools, Altamirano, & D'Esposito, 2006; Frank, Samanta, Moustafa, & Sherman, 2007a).

Third, we investigated learning in a sample of early Huntington's disease (HD) patients, a disease that is associated with a hyper-activation of the 'direct' pathway. Thus, we hypothesized that these patients will be selectively impaired in successful learning from positive PEs.

2. Methods

2.1. General methods

2.1.1. WPT

All three studies (PET, PD & HD) involved the same stimulus-response learning task, a standard version of the WPT (Knowlton et al., 1994; see Figure 1 in Wilkinson et al., 2014), with corrective feedback to ensure learning based on striatal DA transmission. In the PET study, participants also completed a control version of the WPT without corrective feedback. Further, the card patterns in the control task were not related to the outcome.

On each trial, participants were presented with a particular arrangement of cards comprising one, two or three of the four possible tarot cards. Participants were asked to decide whether the presented set of cards predicted sunshine or rain. There were 14 possible arrangements of cards, as the four card and no card patterns were not used. The four cards were assigned with a probability for predicting sunshine of 80%, 60%, 40% and 20%, respectively, and predicting rain otherwise. Prediction probabilities for the presented arrangements of cards were derived from the joint probability distribution of the individual cards they contained (see Table 2 in Wilkinson et al., 2014).

After presentation of the stimuli during each trial, participants were asked to predict the weather on that trial, which required them to classify the card arrangement into one of the two possible outcomes (e.g., rainy/fine). Responses were made either via two response buttons (PET/PD study) or verbally to the experimenter (HD study). Following their response, feedback appeared on the screen depending on whether the response was correct (thumbs up) or incorrect (thumbs down). The feedback and the card arrangement both remained on the screen for a short period. After they disappeared a blank screen preceded the presentation of the next combination of cards. If participants failed to make a response, the card arrangement appeared on the screen for the same duration but no feedback was provided. For more details on the particular task designs used in the respective studies please see the original publications (Jahanshahi et al., 2010 [PD study]; Holl, Wilkinson, Tabrizi, Painold, & Jahanshahi, 2012 [HD study]; Wilkinson et al., 2014 [PET study]).

2.1.2. Computational model

Performance on the WPT relies on updating of outcome predictions and related adaptation of subsequent response behavior. Thus, the task was previously used to assess PE-related learning (Rodriguez, Aron, & Poldrack, 2006). As the aim of our study was to assess differential learning from positive and negative feedback, from a conceptual point of view, our computational model needs to fulfill two criteria: (1) The model incorporates two learning rates, separating learning from positive and negative feedback, and (2) the two learning rates need to be interpretable independently from other model parameters. Consequently, we used a slightly modified version of the classical Q-learning model (Frank et al., 2007b) with two separate learning rates that are fitted independently of the choice consistency parameter β (see Eq. (1)). The latter ensures that the learning rates are statistically independent of the choice consistency parameter, which is not the case when fitting is performed simultaneously. In more detail, our reinforcement learning model consists of four input nodes $I_{i=1,\ldots,4}$ with weighted connections to two output nodes (Q-values) $Q_{j=1,2}$ that represent the presence or absence of the four different cues and the two possible outcomes in the WPT, respectively. On each trial, activity of the output nodes is computed as $Q_j = \sum_i q_{ij} I_i$, where q_{ij} is the weight connecting input node I_i and output node Q_j. Weights are initialized to 0 and updated in each trial by means of $q_{ij}(k+1) = q_{ij}(k) + \alpha^{+/-} S_j(R_j - Q_j) I_i$ where R_j encodes the correct output in this trial and S_j represents the subject's response. The latter is included for allowing the model to simulate the behavior of the individual participant rather than optimal learning. To assess learning from positive and negative PEs separately, we fitted two independent learning rates $\alpha^{+/-}$ for $R_j - Q_j \geq 0$ and $R_j - Q_j < 0$, respectively. For each participant the individual learning rates $\alpha^{+/-}$ were determined that minimized the sum of squared differences between the model's output and the participant's response: $\sum_{jk} (S_{jk} - Q_{jk})^2 \rightarrow \min$, with $j = 1, 2$ and k being the number of trials. In a subsequent step, we modeled each participant's choices of a particular outcome to follow a softmax distribution:

$$P(choice = S_j | Q_1, Q_2) = \frac{\exp\left(\beta Q_j\right)}{\exp(\beta Q_1) + \exp(\beta Q_2)} \text{ with } j = 1, 2 \qquad (1)$$

The choice consistency parameter β was fitted to participants' choices by minimizing the negative log likelihood of the choice probabilities P

$$LL = -\ln\left(\prod_k P_k\left(Q_j\right)\right), \qquad (2)$$

while the two learning rates were held constant at the values optimized in the first step. Model fitting and estimation of all parameters was accomplished by nonlinear optimization.

In order to ensure that the modifications to a standard Q-learning model did not compromise adequate model fit, we compared the model described above with (1) a similar model with only one learning rate instead of two and (2) a Q-learning model with simultaneous fitting of all three free parameters.

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For quantitative model comparison, we performed random-effects Bayesian model comparison (Daunizeau, Adam, & Rigoux, 2014) to estimate exceedance probabilities and expected model frequencies (Stephan, Penny, Daunizeau, Moran, & Friston, 2009). Additionally, we utilized the Bayesian information criterion $BIC = -2*LL + k*ln(n)$ (Schwarz, 1978), where LL is the log likelihood of the model's choice probabilities, k is the number of free parameters of the respective model and $n = 200$ represents the number of trials. Based on BIC we computed ΔBIC values that represent mean differences (per subject) between the respective model and the model with the lowest BIC value. We also computed pseudo-r^2 values as defined in Daw, Doherty, Dayan, Seymour, and Dolan (2006) to test if our model fitted subjects' learning performance above chance level.

In addition to a quantitative model fit comparison, we assessed if the respective models resembled participants' learning performance in a meaningful way. Therefore, we computed linear regression models with participants' mean percent correct responses as dependent variable and fitted model parameters as independent regressors.

Details of the model comparison are presented in Table 1. Across all subjects, model frequencies and exceedance probabilities favor standard QL which was identified as the best fitting model in 46% of participants. However, BIC values are almost identical for the three models and ΔBIC values of 1.76 and .32 do not provide any strong evidence against the two competing models. In addition, pseudo-r^2 values show that all three models fit similarly above chance level. Within all different study populations, the stepwise 2 LR model provides the best or second best model fit, again with pseudo-r^2 values showing that the model fitted subjects' performance above chance level. Importantly, the stepwise 2 LR model explained significant variance in participants WPT performance in all three studies according to regression analyses. Thus, modifications in our new model yield meaningful and independently interpretable parameter estimates without compromising adequate model fit.

2.1.3. *Statistical analyses*

All behavioral results were computed with PASW-SPSS-Statistics 19.0 (IBM Corporation, Somers, NY, USA). A significance criterion of $\alpha = .05$ was used, unless otherwise specified. All significance levels reported are two-tailed.

2.2. *Methods PET study (Wilkinson et al., 2014)*

2.2.1. *Participants*

Seven (3 female) healthy volunteers in the age of 45–70 ($M = 56.86$, $SD = 8.7$) were recruited. None of the participants

Table 1 – Model comparison between the stepwise modeling approach with two learning rates (stepwise, 2 LR) and two alternatives: a model with only one learning rate and stepwise fitting (stepwise, 1 LR) and a model with two learning rates and simultaneous fitting (standard QL).

		Stepwise, 2 LR	Stepwise, 1 LR	Standard QL
All subjects ($n = 63$)	pseudo-r^2	.37	.37	.38
	BIC	11352	11261	11241
	ΔBIC	1.76	.32	–
	Model frequencies	.27	.26	.46
	Exceedance probabilities	.03	.02	.95
	Regression-model	**$R^2 = .65$**	**$R^2 = .14$**	R^2=.05
		$p < .001$	**$p = .01$**	$p = .4$
PET ($n = 7$)	pseudo-r^2	.25	.25	.23
	BIC	1484	1485	1535
	ΔBIC	–	.14	7.29
	Model frequencies	.45	.44	.11
	Exceedance probabilities (%)	.5	.48	.02
	Regression-model	**$R^2 = .96$**	**$R^2 = .97$**	**$R^2 = .96$**
		$p = .01$	**$p = .001$**	**$p = .02$**
PD ($n = 22$)	pseudo-r^2	.23	.29	.21
	BIC	4677	4460	4953
	ΔBIC	9.86	–	22.41
	Model frequencies	.24	.51	.25
	Exceedance probabilities (%)	.05	.9	.05
	Regression-model	**$R^2 = .91$**	$R^2 = .05$	$R^2 = .11$
		$p = 1.17*10^{-9}$	$p = .63$	$p = .53$
HD ($n = 34$)	pseudo-r^2	.47	.46	.51
	BIC	5192	5315	4752
	ΔBIC	7.02	13.62	–
	Model frequencies	.29	.03	.68
	Exceedance probabilities (%)	.01	0	.99
	Regression-model	**$R^2 = .29$**	$R^2 = .07$	$R^2 = .04$
		$p = .02$	$p = .33$	$p = .76$

N.B. *BIC* = Bayesian Information Criterion. Values in bold indicate significant variance explanation. All three tested models showed comparable model fit according to pseudo-r^2 and *BIC* values. While standard QL shows the best fit according to estimated probabilities and model frequencies across all subjects, ΔBIC indicate no strong evidence against the other two models. Importantly, despite comparable model fit, only the stepwise model with two learning rates was able to explain significant variance in participants' WPT performance in all three studies according to regression analyses. LR = Learning rate.

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had any neurological disorder or history of psychiatric illness, drug or alcohol abuse or were on any drug treatments that might influence performance. Participants were asked not to smoke or drink caffeinated drinks for at least 12 h prior to the scan, although we did not control for their average daily consumption of caffeine or nicotine. Participants completed the Beck Depression Inventory (BDI-II) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961, 1996) to preclude signs of depression. The study was approved by the Research Ethics Committee of Hammersmith, Queen Charlotte's and Chelsea and Acton Hospitals Trust. Permission to administer radioactive substances was granted by the Administration of Radioactive Substances Advisory Committee of the UK. All participants gave written informed consent to take part in this study in accordance with the Declaration of Helsinki. For more details on selected participants, please see Wilkinson et al. (2014).

2.2.2. WPT

All participants completed 400 trials of the WPT in eight blocks of 50 trials each while having a [^{11}C]raclopride PET scan. For more details, see Wilkinson et al. (2014). Notably, here we analyzed participants' task performance across the first four blocks of 200 trials to assess learning, as afterwards participants' performance reached a plateau.

2.2.3. Control task

As for the WPT, the control task comprised 400 trials (of which we analyzed the first 200) that were completed while participants had a [^{11}C]raclopride PET scan. On each trial participants were presented with an arrangement of between one and three of four possible cards, these were in the same positions on the screen as the card arrangements that were used in the experimental conditions. However, here the patterns on the four cards were identical and were not related to any outcomes or followed by corrective feedback. The card arrangements remained on the screen for a fixed period of 7 sec after which they disappeared and the next card arrangement appeared after 2 sec. Participants were required to press a response button with their right index finger to indicate they had seen the card arrangements.

2.2.4. Scanning procedure

All participants underwent [^{11}C]raclopride PET twice within four weeks. On each scanning session the respective task started 5 min before injection of tracer and ended 5 min before completion of [^{11}C]raclopride PET (total duration 60 min). Half of the participants completed the WPT during the first [^{11}C]raclopride PET session and the remainder did the control task first.

2.2.5. PET scanning

As stated in Wilkinson et al. (2014) PET was performed using an ECAT EXACT HR+ (CTI/Siemens 962, Knoxville, TN) tomograph with a total axial field of 15.5 cm 63 transaxial image planes were displayed as 2.46 mm slices with a reconstructed axial resolution of 5.4 mm and a transaxial resolution of 5.6 mm. A 10-min transmission scan was performed prior to injection of the tracer to correct for tissue attenuation of 511 keV gamma radiation. Dynamic emission scans were acquired in three-dimensional mode. The mean injected doses of [^{11}C]raclopride for each group is listed in Table 1 of Wilkinson et al. (2014). Scanning began at the start of tracer infusion generating 20 periods over 60 min. A laptop was used to present the WPT or control task to the participants, and the tasks commenced 5 min before the injection of RAC. RAC was supplied by Hammersmith Imanet.

2.2.6. Image analysis

As stated in Wilkinson et al. (2014) parametric images of [^{11}C]raclopride binding potential (RAC BP_{ND}) were generated using a basis function implementation of the simplified reference tissue model using cerebellar cortex to estimate non-specific tracer uptake (Gunn, Lammertsma, Hume, & Cunningham, 1997). An image of integrated [^{11}C]raclopride signal from 0 to 60 min (an "ADD" or summed image) was also created for each participant. The ADD images were then spatially normalized to an in-house [^{11}C]raclopride template in standard stereotaxic (MNI) space using statistical parametric mapping (SPM2) software (Wellcome Functional Imaging Laboratory, London). The transformation matrices were then applied to the corresponding [^{11}C]raclopride parametric image. A standard region-of-interest (ROI) object map that outlined putamen, heads of caudate nucleus and ventral striatum was defined on the [^{11}C]raclopride template with magnetic resonance imaging guidance. The ROI object map was then applied to the individual [^{11}C]raclopride parametric images to sample RAC BP_{ND}. The investigator analyzing the scans was blinded to the task associated with each scan.

2.3. Methods PD study (Jahanshahi et al., 2010)

2.3.1. Participants

Eleven individuals with a diagnosis of idiopathic PD (8 male) aged between 53 and 73 ($M = 63.5$, $SD = 6.2$) were included. Patients were recruited from the Movement Disorders Clinics at the National Hospital for Neurology and Neurosurgery. They met Parkinson's Disease Society Brain Bank diagnostic criteria for PD (Hughes, Daniel, Kilford, & Lees, 1992). Disease duration ranged from 3 to 37 years ($M = 13.2$, $SD = 10.7$). Despite the wide range of disease duration, the majority of patients was in the early stage of PD, with disease durations of less than 14 years. Two patients, however, had relatively long disease duration of 30 and 37 years. Without those two patients the average disease duration was 8.76 years. Importantly, the results reported below did not change when the two subjects were excluded from the analyses (or disease duration was included as a covariate). All patients were non-demented as demonstrated by scores >26 on the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and non-depressed according to scores <18 on the BDI (Beck et al., 1961). The MMSE has been recommended as a screening tool for identifying cognitively impaired patients and, specifically, for characterizing PD associated dementia (e.g., Dubois et al., 2007). All patients were treated with levodopa (Sinemet, Madopar) and were responding well and stable on their medication doses. PD patients were matched with the controls for age, education, sex, verbal IQ and dementia based on MMSE scores. For further details regarding the patient sample please see Jahanshahi et al. (2010).

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Further, thirteen healthy volunteers (5 male) aged between 44 and 69 ($M = 60.0$, $SD = 9.7$) took part in the study. None of the controls had any neurological disorder, psychiatric illness, head injury, history of alcohol or drug abuse, or depression (BDI). For more details see Jahanshahi et al. (2010).

2.3.2. Task procedure

All participants performed 200 trials of the WPT separated into four blocks of 50 trials each (for more details see e.g., Jahanshahi et al., 2010) twice with different but parallel stimuli and outcomes (rainy/fine or cold/hot) presented on each occasion. Six of the PD patients were tested *off* medication first and the remainder was tested *on* medication first. PD patients completed the off and on medication conditions on 2 separate days, with a mean delay of 11.9 days ($SD = 6.9$) in between. Controls completed the two assessments on the same day, separated by a long lunch break.

2.4. Methods HD study (Holl et al., 2012)

2.4.1. Participants

Eighteen individuals (9 male) with genetically proven HD [for genetic details, see Table 1 in Holl et al. (2012)] aged between 32 and 68 ($M = 50.28$, $SD = 10.2$) took part. Patients were recruited from the HD clinic at the National Hospital for Neurology and Neurosurgery and from the HD clinic at the Department of Psychiatry at Graz Medical University. Patients were in the early stages of the disease, with an average score on the Unified Huntington's Disease Rating Scale Total Functional Capacity (UHDRS TFC, Shoulson & Fahn, 1979) of 11.61 ($SD = .3$). The UHDRS motor score (Hungtington Study Group, 1996) was used for assessment of motor symptoms, patients presented with an average score of 20.39 ($SD = 10.4$). All patients were non-demented, as demonstrated by scores >24 on the MMSE. The MMSE has been recommended as a screening tool for identifying cognitively impaired patients (e.g., Dubois et al., 2007). In addition, the patients were screened for clinical depression on the BDI. One patient had a BDI score of 18 and one had a score of 24 (moderate depression), but neither met the criteria for clinical depression in a psychiatric interview.

Eighteen healthy volunteers (9 male) aged between 30 and 74 ($M = 50.00$, $SD = 13.3$) took part in the study. Controls were recruited via an advertisement at a local adult education center in London and a participant recruitment website. Prior to participation in the study, controls were interviewed and screened for suitability. None of the controls had any neurological disorder, psychiatric illness, head injury, or history of alcohol or drug abuse. Further screening of the controls was achieved through completion of the MMSE and BDI, on which the controls had mean scores in the normal range.

For further information on the patients and controls sample, please see Holl et al. (2012).

Unfortunately, we had to exclude one healthy participant and one HD patient from modeling analyses, due to partial data loss.

2.4.2. Task procedure

All participants performed 150 feedback-based trials of the WPT separated in three blocks of 50 trials each (for more details see Holl et al., 2012).

3. Results

3.1. Results PET in healthy volunteers

3.1.1. Striatal ^{11}C-raclopride binding

Here, we only report on post-hoc comparisons of RAC BP_{ND} between the WPT and baseline task across ROIs utilizing independent samples *t*-tests. For more details on analyses regarding RAC BP_{ND} data, we refer the reader to Wilkinson et al. (2014).

There was a trend for a reduction in RAC BP_{ND} in the right and left ventral striatum when performing the WPT compared to the control task [13.4% reduction in the right, $t(6) = -2.01$, $p = .09$, 6.0% reduction in the left, $t(6) = -2.18$, $p = .07$], indicating release of synaptic DA during feedback-based stimulus-response learning. This comparison did not trend towards significance for any other region, left putamen ($t(6) = -1.15$, $p = .29$), right putamen and right and left caudate (all ts < 1). For subsequent analyses we use the mean baseline and % change in RAC BP_{ND} of left and right ventral striatum (9.7%).

3.1.2. Behavioral data

As mentioned previously, in the original paper (Wilkinson et al., 2014) WPT mean proportion of correct responses across 8 blocks of 50 trials was analyzed. Here, we only analyzed participants' WPT performance across the first four blocks, as we were interested in the initial learning phase of the task. For this purpose, we utilize a repeated measures Analysis of Variance (ANOVA) model with within-subjects factor block (4 levels). In addition, to assess the time of emergence and progression of learning across blocks in this condition, mean proportion of correct responses per block was compared to chance (50%) for all four blocks using one sample *t*-tests. Following Bonferroni corrections we adopted a significance threshold of $\alpha = .0125$.

Although the repeated measures ANOVA reported no significant differences between task-blocks [$F(3,6)=1.6$, $p = .23$] on learning performance, there was a trend for a linear association [$F(1,6)=4.47$, $p = .08$], indicating that participants' WPT performance increased across the initial four task-blocks. In line, participants' proportion of correct responses was significantly better than chance from block three onwards: [b1: $t(6)=3.31$; b2: $t(6)=3.08$; b3: $t(6)=3.72$, $p < .01$; b4: $t(6)=3.77$, $p < .01$].

3.1.3. Modeling

As learning the WPT was related to DA transmission within the ventral striatum only, we focus on ventral striatal RAC BP_{ND} in subsequent analyses. We utilized two separate regression models to test our hypotheses regarding the associations of learning from positive and negative PEs with averaged ventral striatal RAC BP_{ND} measures.

The first regression model included positive learning rate as dependent variable and baseline RAC BP_{ND} and % change in RAC BP_{ND} as regressors to test for a positive linear association between positive learning rates and phasic DA transmission. The second model included negative learning rate as dependent variable and baseline RAC BP_{ND} as well as

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RAC BP^2_{ND} as regressors to test for a quadratic (inverted u-shaped) association between height of negative learning rate and tonic DA levels in the ventral striatum. In addition, we computed a regression model with positive learning rate as the dependent variable and ventral striatal dopaminergic asymmetry as a regressor. Asymmetry was assessed by percent difference between left and right baseline RAC BP_{ND}. Finally, we tested a possible quadratic (inverted u-shaped) association between modeled choice consistency and tonic DA release with a model similar to the second one. All regression models included age as a covariate to control for age related effects in DA transmission.

In line with our first hypothesis, learning from positive PEs showed a significant negative linear association with the % change in RAC BP_{ND} within ventral striatum for WPT compared to control task assessment ($R^2 = .89$, $\beta = -.94$, $p = .001$, Fig. 1A), indicating a positive linear association of phasic DA release and learning from positive PEs. Further, modeled negative learning rates showed a significant negative quadratic relationship with the baseline RAC BP_{ND} ($R^2 = .89$, $\beta = -.74$, $p = .005$, Fig. 1B) in ventral striatum. In addition, we observed a significant negative linear relationship between positive learning rate and asymmetry between left and right ventral striatal baseline RAC BP_{ND} ($R^2 = .81$, $\beta = -.9$, $p = .006$, Fig. 1C). Choice consistency was negatively associated with baseline RAC BP_{ND} ($R^2 = .87$, $\beta = -.91$, $p = .006$) in a quadratic model.

3.2. Results PD

3.2.1. Behavioral data

As reported (Jahanshahi et al., 2010) WPT performance (averaged over 200 trials) of healthy controls did not differ significantly across sessions [session 1 (2): .68 (.72), $t(12) = -.99$, $p = .34$]. Therefore, their data were collapsed across assessments to compare PD patients' overall learning performance *on* and *off* medication with the performance of healthy controls. When *off* medication, patients' performance was comparable to the controls' combined performance [$t(35) = -.92$, $p = .36$] indicating that DA levels within ventral striatum were still in an optimal range for learning the WPT. In contrast, when PD patients were tested *on* medication, their overall performance was significantly worse than the controls' combined performance [$t(35) = -2.26$, $p = .03$].

To assess the impact of levodopa on PD patients' performance an repeated measures ANOVA was performed on mean proportion of correct responses with medication (*on vs off*) as a within subjects variable and order of testing (*on* first *vs off* first) as a between groups variable. This analysis revealed a significant main effect of medication [$F(1,9)=11.45$, $p = .01$]. A post-hoc paired sample *T*-test revealed that PD patients showed better WPT performance *off* (.67) than *on* (.63) medication [$t(10)=2.72$, $p = .02$, Fig. 2A]. There was no significant main effect of order [$F(1,9)=1.64$, $p = .23$] or order × medication interaction [$F(1,9)=4.89$, $p = .06$].

3.2.2. Modeling

To test our hypothesis that PD patients *on* medication are specifically impaired in learning from negative PEs we set up a repeated measures ANOVA with within-subjects variable medication (*off/on*). As gender is known to modulate PD onset and phenotype (Haaxma et al., 2007; Van Den Eeden et al., 2003) we included it as a covariate. As there was no effect of order in the behavioral data we did not include this variable. We observed a significant main effect of medication on participants' negative learning rates [$F(1,9)=7.57$, $p = .02$, Fig. 2B]. A similar model yielded no significant effect of medication on positive learning rates [$F(1,9)=.07$, $p = .79$]. There was no significant effect of medication on modeled response consistencies [$F(1,9)=.16$, $p = .23$].

3.3. Results HD

3.3.1. Behavioral data

We utilized a repeated measures ANOVA with within-subjects variable block (1–3) and between-subjects variable group (patients/controls). As the sample size (18) was reasonably large and there is recent evidence of gender-related differences in HD phenotype (Zielonka et al., 2013), we also included gender into our model. The analysis revealed a significant effect of block [$F(2,64)=17.1$, $p < .001$] indicating that, on average, participants learned the task. Learning performance in general was different for healthy controls compared with HD patients as revealed by a significant main effect of group [$F(1,32)=5.64$, $p=.02$]. The between-subject interaction of group × gender was significant [$F(1,32) = 4.9$, $p = .03$, Fig. 3A], showing that learning performance in general was different between gender-specific subgroups. In line, the three-way interaction of block × group × gender exhibited a trend for significance [$F(2,64)=2.87$, $p = .06$], indicating that learning was different between gender specific control and HD groups. All other interactions were non-significant.

In view of the significant gender × group interaction, post-hoc independent samples *t*-tests revealed that female HD patients showed lower over-all learning performance than female control participants [HD = .72, control = .61, $t(16)=3.5$, $p = .003$], whereas there was no difference for men [HD = .7, control = .7, $t(16)=.11$, $p = .92$].

3.3.2. Modeling

We computed two separate ANOVAs for positive and negative learning rates as dependent variables with group and gender as between-subject factors. There was no significant main effect in either model, but the group × gender interaction had a significant impact on participants' positive learning rates [$F(1, 30)=5.15$, $p = .03$, Fig. 3B], whereas there was no such effect on learning rates from negative PEs [$F(1,30)=.15$, $p = .7$]. Post-hoc independent samples *t*-tests revealed that female HD patients showed elevated learning from positive PEs compared to controls [$t(15)=2.13$, $p = .05$]. There was no difference between male patients and control participants [$t(15)=.98$, $p = .34$]. In addition, positive learning rates showed a positive linear association with assessed motor symptom severity across all HD patients [$R^2 = .3$, $\beta=.55$, $p = .02$, Fig. 3C]. Motor symptom severity did not differ significantly between male and female HD patients [$t(15)=.24$, $p = .81$].

There was no significant main effect of group [HD/controls, $F(1,30)=2.14$, $p = .15$] or a group × gender interaction [$F(1,30)=2.78$, $p = .11$] on participants' response consistencies between HD patients and healthy controls.

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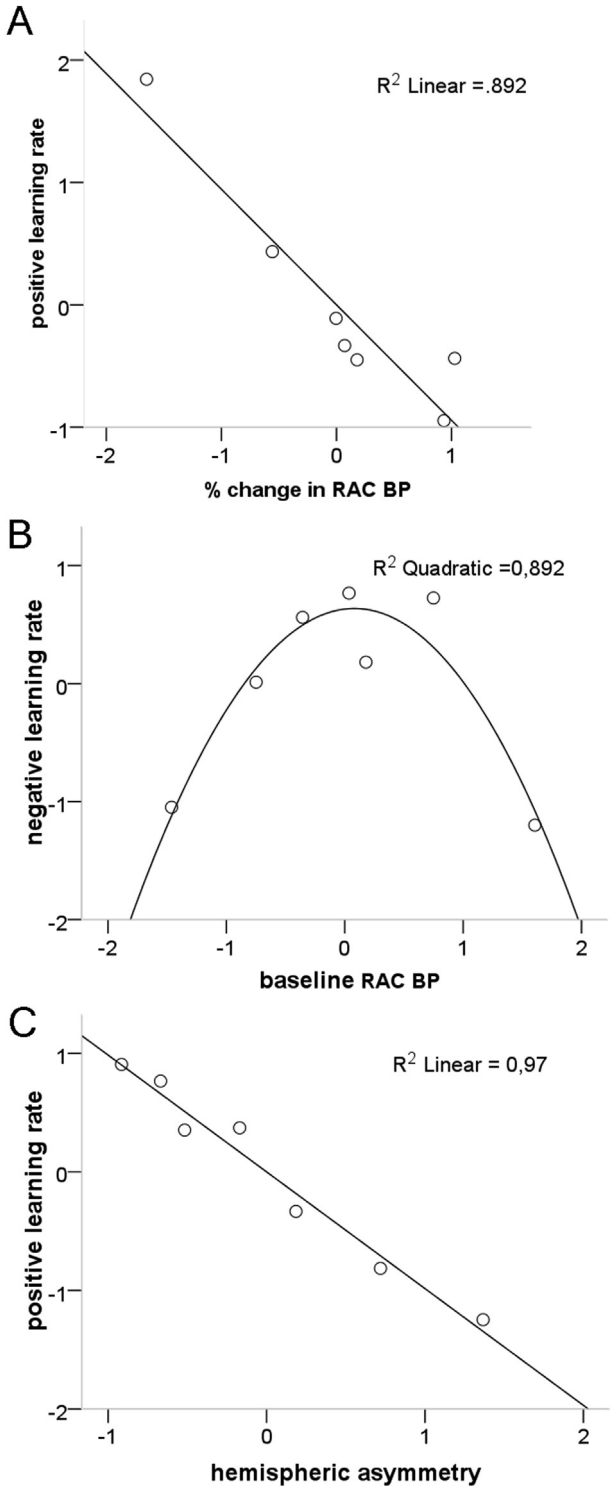

Fig. 1 – Association between phasic and tonic dopaminergic signaling and learning on the Weather Prediction Task. (A) Dopamine release, as measured by the change in [^{11}C]raclopride binding potential between WPT control and feedback sessions, is positively associated with the ability to learn from positive prediction errors (PEs) in healthy subjects. (B) Dopaminergic tone, as estimated by baseline [^{11}C]raclopride binding potential, is associated with learning from negative PEs in an inverted u-shaped manner. (C) Hemispheric asymmetry between left and right ventral striatum in dopaminergic tone is negatively associated with learning from positive PEs.

4. Discussion

4.1. *Summary*

For optimal functioning within our complex environment procedural learning of appropriate stimulus-response associations is crucial. Positive and negative PEs serve as neural teaching signals within distinct pathways to update these associations and optimize our subsequent behavior. Positive PEs are reflected in an increase in the phasic firing rate of dopaminergic neurons, whereas negative PEs are reflected in transient dips of the tonic DA signal (Schultz et al., 1997; Tobler, Dickinson, & Schultz, 2003). Here, we assessed stimulus-response learning from positive and negative PEs on the probabilistic WPT using computational modeling. We included data from healthy volunteers and from two samples of patients exhibiting specific alterations in predominantly one of the two segregated pathways. Consequently, the different patient populations should reveal disturbances mainly in either learning from positive or learning from negative PEs.

Taken together, our computational modeling results indicate that learning from positive and negative feedback on the WPT is intimately linked to different aspects of dopaminergic transmission. Phasic dopaminergic responses are predictive of learning from positive feedback on the WPT. In healthy individuals, we observed a linear association between difference in RAC BP as a measure for striatal DA release and positive learning rate on the WPT. Further, asymmetry between baseline DA tone in left and right ventral striatum is negatively associated with learning from positive PEs. Female patients with early progression of HD, which is characterized by a hyper-activation of the 'direct' pathway, exhibited exaggerated learning rates from positive feedback. In contrast, dopaminergic tone predicts learning from negative feedback on the WPT, as indicated by an inverted u-shaped association observed with baseline RAC BP in healthy controls and the difference between PD patients *on* and *off* medication.

4.2. *Learning from negative PEs on the WPT*

Dopaminergic tone predicts learning from negative feedback on the WPT, as indicated by an inverted u-shaped association observed with baseline RAC BP in healthy controls. This is in line with previous research showing that avoidance learning was associated in an inverted u-shaped manner with D2 receptor availability (Cox et al., 2015). Importantly, because [^{11}C]-raclopride is competing with endogenous DA, D2 receptor availability as estimated by RAC BP may depend on both, the occupancy of receptors by endogenous DA and D2 receptor density. Thus, baseline BP may in part be interpreted as reflecting dopaminergic tone. It has been shown that either too low or too high tonic DA levels impair behavior in different cognitive domains (Cools & D'Esposito, 2011; Floresco, 2013). Non-optimal DA levels seem to affect particularly the

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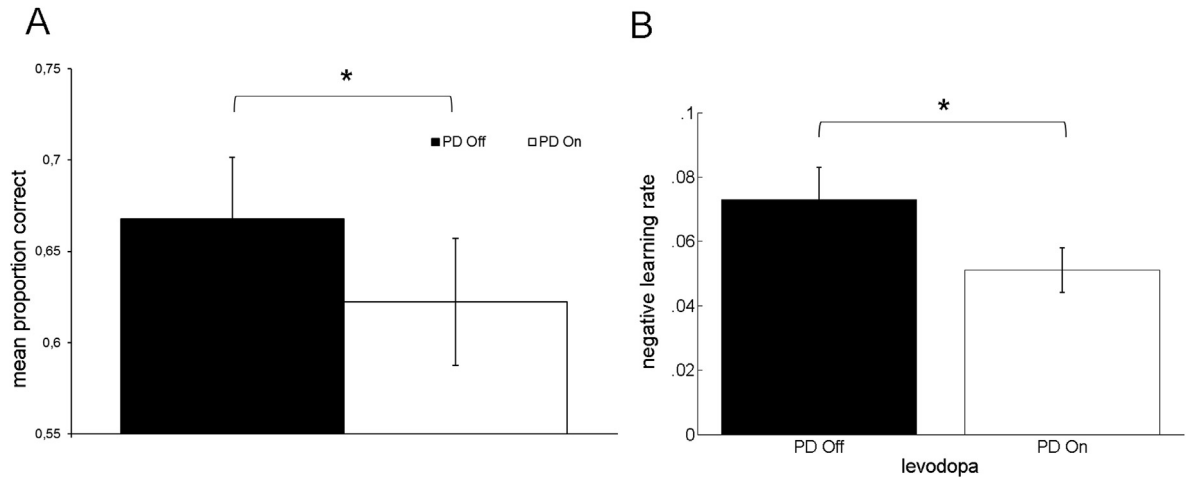

Fig. 2 – Behavioral differences between *off* and *on* dopaminergic medication in patients with Parkinson's disease on the Weather Prediction Task. (A) Mean proportion correct responses on the Weather Prediction Task for Parkinson patients *off* and *on* dopaminergic medication. (B) Parkinson patients *on* dopaminergic medication are impaired in learning from negative prediction errors on the Weather Prediction Task compared to *off* medication. Asterisk indicates $p < .05$.

capability of detecting dips in tonic dopaminergic signaling and, consequently, may thus alter learning from negative PEs in particular. In healthy volunteers, depletion of DA precursors specifically improves avoidance learning, presumably via a better signal-to-noise ratio due to a reduction of DA tone in the 'indirect' pathway, but leaves approach learning unaffected (Cox et al., 2015). Our results indicate that in PD patients, however, a drastic increase in the level of ventral striatal DA impairs learning from negative PEs. L-DOPA has previously been shown to specifically impair reversal learning (Cools, Barker, Sahakian, & Robbins, 2001) and disrupt activity in the nucleus accumbens in PD patients (Cools, Lewis, Clark, Barker, & Robbins, 2007). Since dopaminergic tone is associated with the ability to learn from negative PEs in an inverted u-shaped manner, our results suggest that ventral striatal dopaminergic tone in PD patients *off* medication is still preserved at an optimal level. This is corroborated by comparable performance of PD patients *off* medication and healthy controls. Additional administration of L-DOPA then causes a suboptimal increase in DA levels in the ventral striatum, resulting in an impaired ability to detect dips in tonic DA. PD patients in our subject sample also received DA agonists besides L-DOPA (see Jahanshahi et al., 2010). Thus, withdrawal from both or even withdrawal from DA agonists alone might have caused the observed differences in PD patients *off* versus *on* medication (Moustafa, Herzallah, & Gluck, 2012, pp. 1–21). However, our results on differences in PD patients' learning from negative PEs between *on* and *off* medication are consistent with earlier reports on the effects of dopaminergic medication on reinforcement learning in PD patients using different tasks (Bodi et al., 2009; Frank et al., 2007a, 2004). In line, Cools et al. (2006) demonstrated a medication-induced deficit that was restricted to conditions with unexpected punishment and Moustafa, Krishna, Eissa, and Hewedi (2013) reported reduced learning from negative feedback in PD patients under dopaminergic medication compared to unmedicated patients. Additionally, Moustafa et al. observed enhanced learning from positive feedback under dopaminergic medication. Notably, they used a simpler probabilistic stimulus-response learning task with only single cue stimuli. Together, these results suggest that dopaminergic tone predicts the ability to learn from negative PEs on the WPT, both in healthy individuals and in PD patients on dopaminergic medication. Importantly, the specific effect depends on the initial level of DA: Because of the basic non-linear relationship between DA levels and performance, additional heightening or lowering levels of DA might cause suboptimal performance on the WPT.

4.3. *Learning from positive PEs on the WPT*

Learning from positive PEs depends linearly on the magnitude of phasic DA release in healthy volunteers. Importantly, dopaminergic tone seems to be a powerful modulator of phasic DA transmission, as learning from positive PEs was best explained when we took into account both, % change in RAC BP as a measure of phasic DA release during learning and baseline RAC BP as an indicator of density and background stimulation of DA receptors. These results are in line with a previous report demonstrating the direct association between learning from positive feedback and signaling in the 'direct' pathway in healthy volunteers (Cox et al., 2015). In their study, learning to approach options associated with a positive outcome in a probabilistic selection task was linearly associated with D1 receptor density in the striatum.

Further, we found the ability to learn from positive PEs to be negatively associated with the asymmetry between baseline DA tone in left and right ventral striatum in healthy volunteers. Our results are in line with previous findings. Gray (1981) postulated that individual differences in motivational behavior are related to either a bias towards behavioral activation to approach incentives or behavioral inhibition to avoid

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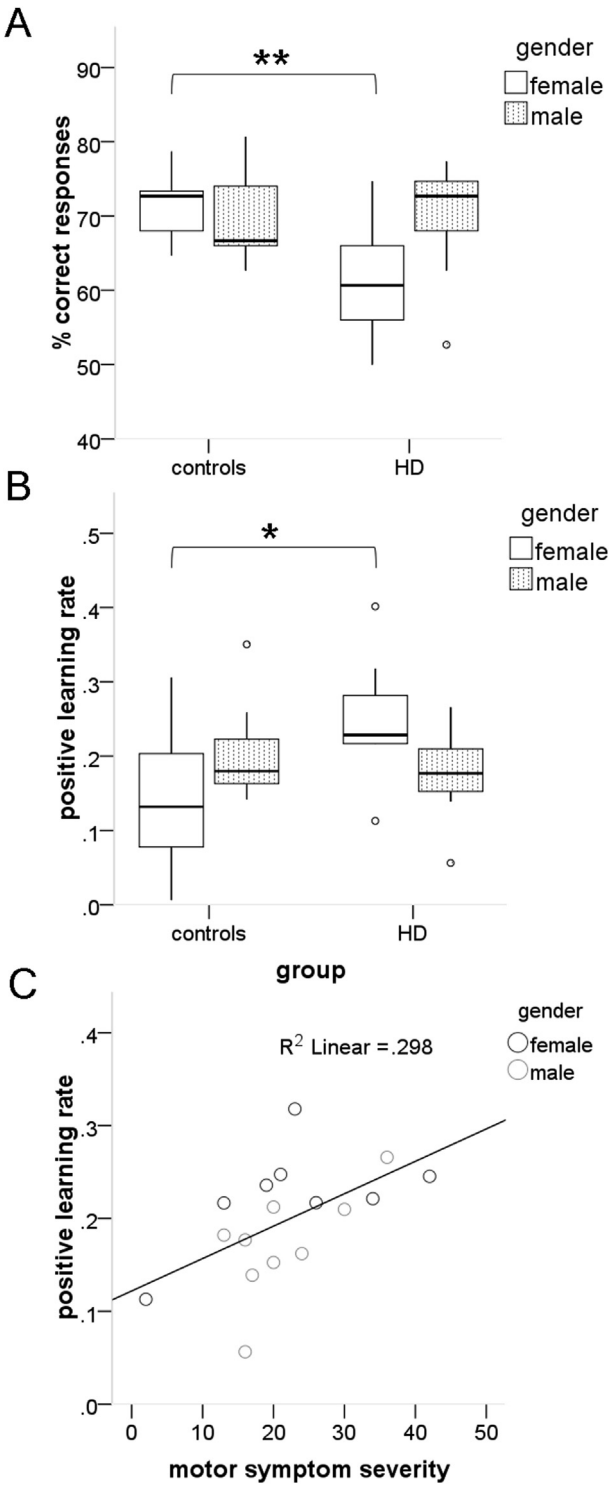

Fig. 3 – Gender-specific behavioral impairment in patients with Huntington's disease on the Weather Prediction Task. (A) Mean proportion correct responses on the Weather Prediction Task for healthy control subjects and early Huntington Disease (HD) patients split by gender. (B) Interaction between group (control/HD) and gender on the propensity to learn from positive prediction errors on the Weather Prediction Task. (C) Positive learning rate is positively associated with motor symptom severity across both genders in patients with early Huntington's disease.

punishment. Stronger approach motivation has been linked to greater left than right prefrontal activation according to Electroencephalography power (e.g., Sutton & Davidson, 1997), as well as PET and functional Magnetic Resonance Imaging-related activation (Murphy, Nimmo-Smith, & Lawrence, 2003; Wager, Phan, Liberzon, & Taylor, 2003). Presumably, this asymmetric activation is related to hemispheric asymmetry in dopaminergic transmission. Hemispheric asymmetry in DA has repeatedly been shown to be associated with approach and avoidance motivation and learning. In healthy volunteers, self-reported motivational bias between approach and avoidance was predicted by the asymmetry of frontal D2 binding (Tomer et al., 2014). Further, striatal and frontal asymmetries in D2 DA receptor binding predicted individual differences in learning from reward versus punishment (Tomer et al., 2014). PD patients with predominantly left hemispheric deficits were less willing to invest effort to maximize gain, indicating a selective impairment in approach motivation. In contrast, PD patients with a right hemispheric deficit exhibited impairments in avoidance motivation (Porat, Hassin-Baer, Cohen, Markus, & Tomer, 2014). Further, these patients were impaired in learning from positive versus negative feedback, respectively (Maril et al., 2013). In contrast to Aberg et al. (2015), who reported a positive association between better learning from positive PEs and functional asymmetry in left and right ventral striatum, our data indicate a negative relationship. This seeming discrepancy can be explained by the indirect modulation of phasic responses by DA tone via inhibitory actions on the presynaptic cell (Dyakonova et al., 2009; Goto et al., 2007).

So what happens if the balance between the integrity of 'direct' and 'indirect' pathways is compromised? Female patients with early progression of HD, which is characterized by a hyper-activation of the 'direct' pathway, exhibited exaggerated learning rates from positive feedback in our study. In HD, a neurodegenerative, autosomal-dominant transmitted neurodegenerative disorder, cell death of striatal neurons already occurs in early and even pre-symptomatic stages of the disease. The progression of neuronal death in the striatum is gradual and proceeds from dorsal to ventral and from medial to lateral (Aylward et al., 2004; Vonsattel et al., 1985). In early stages of HD, cell death primarily affects GABAergic medium-sized spiny neurons within the 'indirect' pathway. Furthermore, HD has been associated with a loss of pre-synaptic D2 auto-receptors, thus impairing the ability of tonic DA to regulate phasic responses (Cepeda, Murphy, Parent, & Levine, 2014). Reduced striatal D2 receptor availability has been reported even in asymptomatic HD patients and mutation carriers, suggesting that dopaminergic signaling is compromised early in HD (van Oostrom et al., 2009; Weeks, Piccini, Harding, & Brooks, 1996). Taken together, this leads to a hyper-activation of the 'direct' pathway already in very early stages of the disease. In line, HD patients in early stages of the disease have been shown to be generally impaired in procedural stimulus-response learning (Holl et al., 2012). Adding to this, our results indicate that in early HD, DA pathways are affected differentially in women and men and that impairments are selective for learning from positive PEs. While we predicted specificity for learning from positive PEs, the finding of a gender-specific effect in patients with early HD is novel. It has

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been proposed that a general gender difference in endogenous DA levels or other aspects of dopaminergic transmission (Kaasinen, Någren, Hietala, Farde, & Rinne, 2001; Laakso et al., 2002; Pohjalainen, Rinne, Någren, Syvälahti, & Hietala, 1998) may account for gender differences in the vulnerability to neuropsychiatric disorders such as depression, schizophrenia or PD (Gillies, Virdee, McArthur, & Dalley, 2014). For HD, however, penetrance and prevalence seems to be equal for both sexes. Interestingly, a large European study showed recently that women with HD exhibited more severe symptoms and a faster progression of the disease (Zielonka et al., 2013), and a large US study found that women have a longer duration of the disease (Foroud, Gray, Ivashina, & Conneally, 1999). Thus, there might be gender differences in the progression of the disease. Our results indicate a more severe impairment in learning from positive PEs in women with HD compared to men. This might be explained by an interaction of disease-specific effects with sex differences in dopaminergic transmission. Women have a higher presynaptic dopaminergic synthesis capacity (Laakso et al., 2002) and show a lower BP for [^{11}C]raclopride, suggestive of a higher striatal DA concentration (Pohjalainen et al., 1998). Further, women have been shown to have higher D2-like receptor BPs than men in frontal cortex, temporal cortex, and thalamus (Kaasinen et al., 2001). Together, these might produce an additive effect on the hyper-activation of the 'direct' pathway, and, in consequence, exaggerated learning from positive PEs especially in women with early HD. However, as positive learning rate was associated with motor symptom severity across all patients, the gender specific effect might alleviate during further progression of the disease. In line with our results, Palminteri and colleagues observed an asymmetry in favor of reward-based relative to punishment-based learning in patients with early compared to late HD and to controls (Palminteri et al., 2012). Specifically, the authors found a higher reward bias and a higher reinforcement magnitude for gains compared to losses. However, learning rates for gain and loss conditions were not different between HD groups or compared to controls in their study. Importantly, the task they used differed from the WPT in that participants had to learn to approach, i.e., select, rewarding options and to avoid, i.e., to not choose, punishing options in different conditions. Taken together, our results indicate that future work should pay special attention to sex differences in HD.

An imbalance between tonic and phasic DA signaling may lie at the heart of alterations in DA-based learning, as has been observed in attention deficit hyperactivity disorder (Badgaiyan, Sinha, Sajjad, & Wack, 2015), depression (Dunlop & Nemeroff, 2007; Mörkl, Blesl, Jahanshahi, Painold, & Holl, 2016), schizophrenia (Brunelin, Fecteau, & Suaud-Chagny, 2013; Juckel et al., 2006), obesity (Frank et al., 2012; Horstmann, Fenske, & Hankir, 2015) or PD patients on dopaminergic medication (Jahanshahi et al., 2010). Further, within healthy volunteers, the layout of the dopaminergic system seems to be intimately linked to the individual level of personality traits such as approach/avoidance bias and impulsivity (Buckholtz et al., 2010; Tomer et al., 2014).

Taken together, our results demonstrate that solving the WPT relies on the integrity of different pathways within the dopaminergic system. In line with our hypotheses, data from healthy individuals, patients with PD *on* dopaminergic medication as well as from patients with HD show that variance within each pathway is linked to specific performance differences when solving the WPT.

5. Conclusions

The present data reveal that the WPT is suitable to disentangle learning from negative and positive feedback with the help of computational modeling. The ability to learn from positive and negative feedback might prove to be a sensitive marker for the integrity of dopaminergic signal transmission. In particular, it might differentiate between the involvement of the 'direct' and 'indirect' dopaminergic pathways. The present data are interesting beyond clinical context in that imbalances of dopaminergic signaling have not only been observed for psychiatric conditions but also for obesity (Horstmann et al., 2015; Kessler, Zald, Ansari, & Cowan, 2014) and adolescence (Luciana, Wahlstrom, Porter, & Collins, 2012). Thus, future work should differentiate between learning from positive and negative feedback since these processes rely on segregated neural mechanisms. In the case of medical conditions, specific learning impairments would point to associated specific neural changes that call for different treatment options.

Author contributions & Funding

DM and Annette Horstmann designed research, MJ, LW and Anna Holl contributed data, DM and JN implemented computational model, DM analyzed data, LD contributed to model comparisons, DM and Annette Horstmann wrote paper. All authors revised and edited the manuscript.

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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 psycho-physiological 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

Table 1 – Subject sample description: Demographic details, questionnaire, working memory and IQ-test data.

	Lean women	Obese women	Lean men	Obese men	H-/F-value	*p*-value
N	15	15	15	13	–	–
Age M (SD)	26.6 (3.6)	28.3 (4.7)	26.0 (3.2)	27.2 (5.3)	$F(3,54) = .78$	.51
BMI M (SD)	21.9 (1.9)	34.1 (2.5)	22.3 (1.5)	34.0 (3.1)	$F(3,54) = 131.02$	$9.16*10^{-25}$
YOE Median (range)	13 (13–13)	13 (10–13)	13 (10–13)	13 (10–13)	$H(3) = 2.24$	.53
BIS-11 M (SD)	60.3 (6.5)	59.1 (8.2)	62.5 (6.8)	58.9 (9.8)	$H(3) = 2.35$	.50
BDI M (SD)	3.9 (3.2)	5.0 (5.4)	4.1 (5.0)	4.4 (4.9)	$H(3) = .98$	.99
WMT M (SD)	19.4 (3.2)	18.2 (3.0)	18.8 (3.6)	20.6 (2.7)	$H(3) = 3.60$	.31
MWT M (SD)	30.4 (3.5)	29.7 (2.5)	30.9 (4.1)	31.8 (2.8)	$H(3) = 1.69$	.64
2-back, d-prime M (SD)	1.4 (.6)	1.5 (.5)	1.7 (.5)	1.3 (.5)	$F(3,46) = 1.69$	.19

Notes: Distribution of age, body mass index (BMI), years of education (YOE), self-reported trait impulsivity (BIS-11), self-report measure of depressive symptoms (BDI), figural intelligence score (WMT), verbal intelligence score (MWT) and 2-back task performance. Abbreviations: N – sample size, M – mean, SD – standard deviation. Tests for group differences are based on Kruskal–Wallis-H-tests (H) and ANOVA (F).

(Beck Depression Inventory (BDI), (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Hautzinger, Bailer, Worall, & F K, 1994), cut-off value 18), a history of neuropsychiatric diseases, smoking, diabetes mellitus type I and II, conditions which are contraindications to MR-imaging, and abnormalities in the T1-weighted MR scan. All subjects completed the task inside the MR scanner between 8 am and 6 pm. They gave written informed consent before taking part in the study and were reimbursed with 8 €/hour and an additional amount of up to 4 € in relation to task performance.

2.2. *Weather Prediction Task*

The Weather Prediction Task (WPT (Knowlton et al., 1994)) and behavioral data acquisition were implemented in Presentation 14.7 (Neurobehavioral Systems Inc., Albany, CA, USA). The WPT (Fig. 1A) is a well-established implicit stimulus-response learning task that is used to assess fronto-striatal dopaminergic system function and learning from PEs. WPT trials started with the presentation of a specific stimulus pattern. Subjects then had to decide whether the stimulus pattern predicted sun or rain. After responding, participants received feedback according to the probability distribution of the trial's stimulus pattern. Participants performed 200 WPT trials interleaved with 60 motor-baseline trials, separated into four functional runs of 50 (15 baseline) trials each. Each of the 14 different stimulus patterns consisted of one, two, or three out of four different cues and they were distributed throughout the task according to the scheme in Knowlton et al. (1994). Four cards showing one of the suits (diamonds, clubs, hearts or spades) were used as cues. Cues were assigned with a probability for predicting sunshine of 80%, 60%, 40% and 20%, respectively, and predicting rain otherwise (Poldrack et al., 2001). Stimuli were presented for 3,000 ms. Following participants' response, the stimulus pattern stayed on the screen along with the correct outcome and an emoticon indicating correct or false response for 1,000 ms. Each trial was followed by a fixation cross displayed for 1,000 ms–5,000 ms. Motor-baseline trials differed in that stimuli consisted of three simple cards, each displaying a black square that was presented on the screen together with the word 'LEFT' or 'RIGHT', indicating that subjects should press the corresponding button. Trial order and cue positioning on the screen were pseudo-randomized. Prior to the actual fMRI session, participants completed a short training session consisting of ten prediction and two motor-baseline trials to familiarize them with the task. Cue-outcome associations were different during the training and the fMRI session.

2.3. *Reinforcement learning model*

Performance in the WPT relies on PE-related updating of outcome predictions and associated adaptation of subsequent response behavior (Mathar et al., 2017; Rodriguez et al., 2006). We expected attenuated learning from negative PEs and intact learning from positive PEs in obese compared with lean subjects. During learning the task, subjects experience positive PEs in trials in which the outcome exceeds their expectancy, i.e., in trials in which subjects have not yet built strong stimulus–outcome associations and respond correctly. In contrast, subjects experience a negative PE whenever their outcome prediction is wrong. Importantly, the identity of the classification outcome, i.e., sun or rain, is not systematically associated with the valence of the prediction error. Further, performance on the WPT may not only depend on learning from negative and positive PEs but also on response consistency. As the primary aim of our study was to assess differential learning from positive and negative PEs, from a conceptual point of view, our computational model needs to fulfill two criteria: (1) The model incorporates two learning rates, separating learning from positive and negative feedback, and (2) the two learning rates need to be interpretable independently from the model parameter mimicking response consistency. Consequently, we utilized a slightly

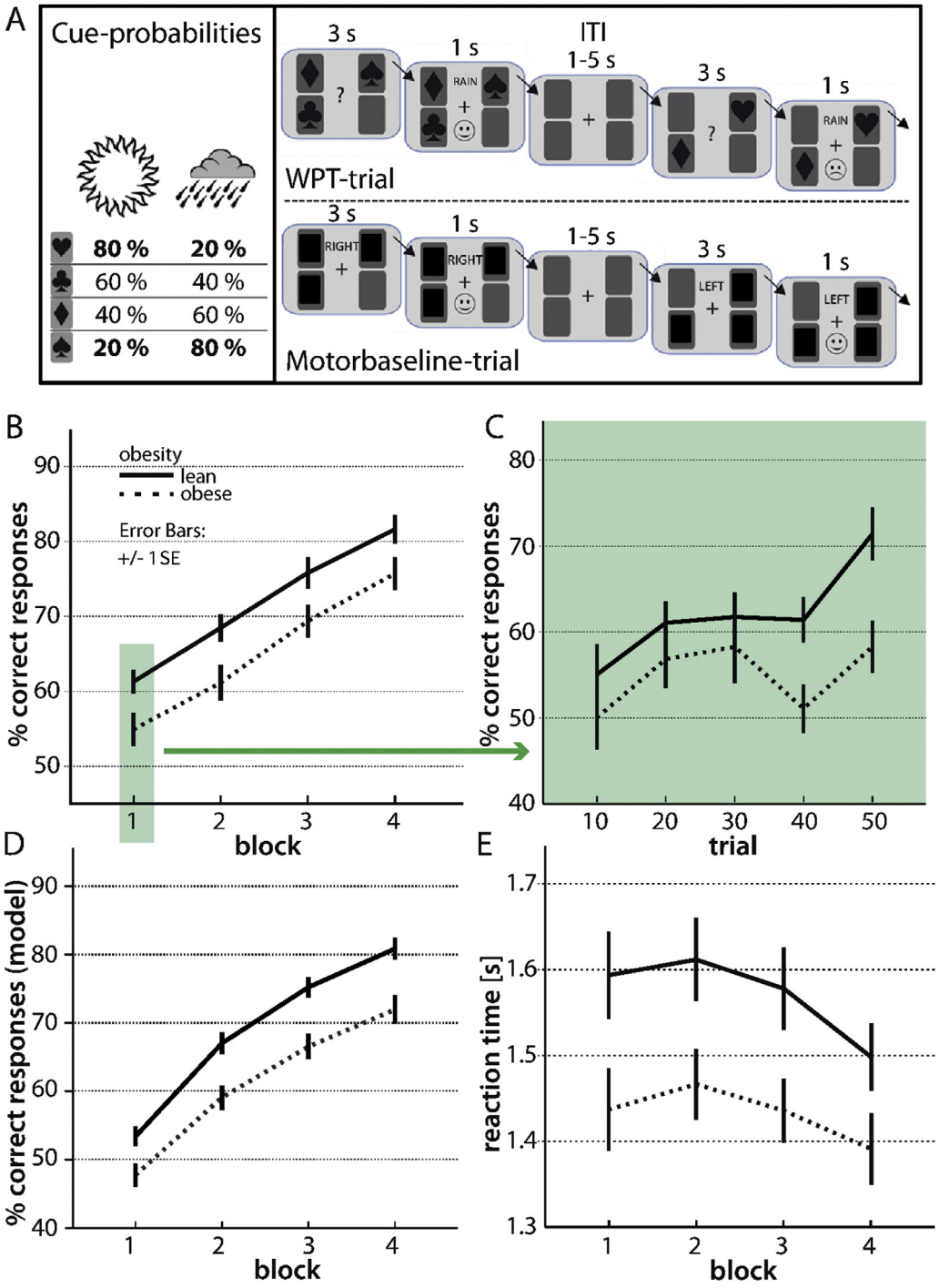

Fig. 1 – A) Schematic representation of cue-outcome probabilities (left) and prediction as well as motor-baseline trials (upper/lower right) in the Weather Prediction Task (WPT); ITI = Inter trial interval. B) Learning performance (percentage of correct responses) of lean (30) and obese participants (28) over the four task blocks C) and zoomed in on the first 50 trials (green inset). D) Simulated learning performance of the reinforcement learning model, separated for lean and obese participants over the four task blocks. E) Reaction time of lean and obese participants over the four task blocks.

modified version of a classic Q-learning model, that we recently employed to differentially assess the associations between learning from positive and negative PEs, and dopaminergic transmission during learning in healthy subjects, and in Parkinson's and Huntington's disease patients (Mathar et al., 2017). To ensure that the two learning rates are statistically independent from the choice consistency parameter, the parameters are fitted in subsequent steps.

Across subjects, our model explained 92% of the variance in subjects' choice behavior. To further assess model

adequacy, we compared it to three additional computational models by means of Bayesian Model Comparison (Daunizeau, Adam, & Rigoux, 2014; Stephan, Penny, Daunizeau, Moran, & Friston, 2009), in order to select the model that optimally captures subjects' behavior in the WPT (Table 2).

2.4. Strategy modeling

Stimulus-outcome associations in the WPT can be learned via different strategies, such as concentrating on individual cues even within complex stimulus patterns or trying to integrate information from multiple cues. We used a computational model (Meeter, Myers, Shohamy, Hopkins, & Gluck, 2006) to infer which strategies subjects employed to solve the task. The strategy model facilitates a maximum likelihood approach to fit subjects' responses to eleven predefined strategies (Meeter et al., 2006). Each strategy stipulates a disposition for predicting sun/rain for each of the 14 different stimulus patterns. One of the eleven strategies predicts sun/rain for every pattern with a probability of 50% and is thus referred to as random-like. The best model fit for each trial is derived considering a moving window of 25 trials centered on trial 13. After model fitting, strategies were grouped into three categories: (i) simple single-cue strategies in which only single-cue patterns or only single cues within a multi-cue pattern are considered for learning, (ii) more complex strategies necessitating information integration of multiple cues, and (iii) random-like strategy. The application of a random-like strategy reflects the fact that a subject has not formed strong predictions for the presented stimuli and, accordingly, might be guessing, might be exploring, or might not be able to maintain consistent behavior.

2.5. Behavioral data analyses

All behavioral results were computed with PASW-SPSS-Statistics 19.0 (IBM Corporation, Somers, NY, USA). Subjects' prediction accuracy was determined utilizing a maximizing metric, i.e., prediction probabilities of the stimulus patterns were translated into binary outcomes and matched with subjects' responses. Thus, in each trial, a response was counted as correct if it matched the most probable stimulus–outcome association. Additionally, we investigated participants' response consistency by assessing the relative number of response switches from sun to rain and vice versa for every stimulus pattern shown throughout the task.

Repeated measures (rm) ANCOVA models were used to assess group differences in learning performance, reaction times (RTs), response consistency and strategy use with within-subject factor task block (1–4) and between-subject factors gender and obesity, including trait impulsivity as a covariate. We further included age as a nuisance variable to account for age-related variance in our data. The same model was applied to test differences in learning rates related to learning from positive as compared to learning from negative PEs, with within-subject factor feedback valence. Obesity-related differences in modeled learning rates (separated for positive and negative PEs), response consistency, and prediction error strengths were assessed using ANCOVAs, incorporating the same factors and covariates as in the rm analyses. Bivariate Pearson's correlation analyses utilizing linear models were computed to further investigate the impact of individual prediction error strength on task performance, corrected for multiple comparisons. Pearson's correlation analyses were further used to assess the associations between PE modulated functional coupling and learning performance, based on strong a priori hypotheses. Gaussianity and heteroscedasticity of variances was confirmed prior to all statistical tests.

2.6. FMRI data acquisition

Imaging was performed with a whole-body 3 T TIM Trio scanner (Siemens, Erlangen, Germany) and a 12-channel head-array coil. Acquisition of whole-brain functional images was achieved with a T2*-weighted standard EPI sequence (30 axial slices, TR = 2,000 ms, TE = 30 ms, flip angle = 90°, spatial resolution = 3 × 3 × 4 mm^3, including 1 mm gap). An MR-compatible mirror enabled the subjects to follow the task

Table 2 – Reinforcement learning model comparison.

	Stepwise QL, 2 lr	Standard QL, 4 input nodes	Standard QL, 14 input nodes	Stepwise QL, 1 lr
BIC	12530	12856	13066	12797
ΔBIC	–	5.62	9.24	4.6
Model frequencies	.93	.02	.03	.02
Exceedance probabilities	1	0	0	0
$\alpha^+(\alpha)$ – correlation with performance	$R^2 = .16$, $p = .0006$	$R^2 = .02$, $p = .25$	$R^2 = .02$, $p = .28$	$R^2 = .74$, $p = 3.7*10^{-15}$
α^- – correlation with performance	$R^2 = .5$, $p = 6.4*10^{-9}$	$R^2 = .02$, $p = .29$	$R^2 = .002$, $p = .77$	–
β – correlation with response consistency	$R^2 = .9$, $p = 4.5*10^{-28}$	$R^2 = .12$, $p = .007$	$R^2 = .02$, $p = .29$	$R^2 = .88$, $p = 9.0*10^{-28}$
Regression-model	$R^2 = .92$, $p = 8.0*10^{-31}$	$R^2 = .14$, $p = .01$	$R^2 = .02$, $p = .23$	$R^2 = .91$, $p = 3.45*10^{-30}$

Notes: Model comparison between the four assessed model architectures. The first three Q-learning (QL) models contain two learning rates, for learning from positive (α^+) and negative PEs (α^-) separately, and a temperature parameter β. The fourth model is similar in model architecture to the first model but has only one learning rate (lr). The stepwise QL model with separate fitting of two learning rates and a consistency parameter reveals the lowest Bayesian information criterion (BIC) and superior model fit according to estimated model frequencies and exceedance probabilities. It also yields meaningful model parameters that correlate with subjects' learning performance and response consistency and explains 92% of subjects' response behavior.

on a screen located outside the magnet and subjects responded via a two-button keypad. Additional high-resolution T1-weighted images were acquired utilizing a MPRAGE sequence (TR = 1,300 ms, snapshot FLASH, TE = 3.93 ms, flip angle = 10°, image matrix = 256 × 240, FOV = 256 × 240 mm^2, spatial resolution = 1 × 1 × 1.5 mm^3) for spatial localization.

2.7. FMRI preprocessing and modeling

Preprocessing and analysis of the event-related fMRI data was performed using the SPM8 software package (Welcome Trust Centre for Neuroimaging, UCL, London, UK) run within MatLab 7.7 (Mathworks Inc., Sherborn, MA, USA). Data from each of the four functional runs were preprocessed including realignment, unwarping, slice time correction, and nonlinear normalization to a standard template (Montreal Neurological Institute, MNI). For normalization purposes, individual high-resolution T1-weighted images were used which had been co-registered during spatial realignment to the individual mean EPI. Normalized images were resliced to a voxel size of 3 × 3 × 3 mm^3 and spatially smoothed with a three-dimensional 8 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. Both event types (WPT and motor-baseline) were modeled utilizing delta functions at each stimulus onset and convolved with the canonic hemodynamic response function (HRF) and its first derivative in order to account for temporal differences in the hemodynamic response between brain regions. In consideration of the number of conditions and their duration specific to our task-design, we applied a temporal high-pass filter of 100 sec to increase the signal-to-noise ratio.

2.8. First-level fMRI modeling

Individual subject data was modeled using three separate general linear models (GLMs) that were computed independently. The first GLM was applied to identify BOLD signal changes during cue-onset elicited by stimulus presentation of the two event-types WPT and motor-baseline. Two parametric modulators, stimulus complexity (1, 2, or 3 visible cues) and individual reaction times (RTs) per trial, were included as covariates. Trials in which participants responded too slowly, i.e., with RTs longer than 3,000 ms, and trials in which subjects did not respond at all, were excluded from the analysis. Contrast images were computed by subtracting activation related to motor-baseline from activation related to stimulus presentation in WPT trials. A further contrast image was computed for the parametric modulator 'stimulus complexity' to assess which neural structures are differentially activated in complex compared with simple stimulus-patterns.

The second GLM was designed to assess striatal activation related to PE coding during feedback. BOLD signal images were modeled at feedback onset and masked for dorsal and ventral striatal nuclei, as both are known to play pivotal roles in signaling PEs (McClure et al., 2003; O'Doherty et al., 2003). Globus pallidus, nucleus caudatus and putamen masks were derived from the WFU Pickatlas toolbox within SPM 8. These masks were merged with a mask of nucleus accumbens obtained from the Harvard–Oxford Subcortical Structural Atlas within FSL 4.1. The model contained a regressor with subject- and trial-specific signed PE values from the reinforcement learning model and a second regressor with ones at feedback onset and zeros otherwise to control for feedback-related activation.

The third GLM implemented a psycho–physiological interaction (PPI) analysis (Friston et al., 1997) to assess PE-related changes in functional connectivity between ventral (dorsal) striatum and other brain areas subsequent to feedback onset. ROIs within ventral striatum/dorsal striatum (8 mm spheres, centers: [±9, 9, −8] ([±28, −4, 2])) were obtained following a recent meta analysis and a resting-state functional connectivity study regarding striatal subdivisions (Di Martino et al., 2008; Postuma and Dagher, 2006). Following an approach previously proposed by Park et al. (2010), time series from the two clusters within left and right ventral (dorsal) striatum were extracted, averaged over both hemispheres and normalized. These time series were subsequently multiplied with condition vectors containing ones for 6 TRs after feedback onsets that elicited a positive or negative PE and zeros otherwise. The resulting vectors were used as PPI regressors together with the feedback-related onset vectors convolved with the HRF to account for feedback-related BOLD activation.

2.9. Second-level fMRI analysis

We computed four separate general linear mixed effects models, based on the contrast images of the first level analyses. The first model was based on the prediction formation related contrast to assess BOLD activation differences during stimulus onset of WPT compared with motor-baseline trials in lean compared with obese subjects. A full-factorial GLM design was employed with between-subject factors obesity and gender and within-subject factor task block. The second model was based on the parametric modulator 'stimulus complexity'. This model aimed at identifying brain regions that show increasing BOLD activation with increasing stimulus complexity (number of cues) and obesity-related differences therein. A full-factorial GLM was utilized with between-subject factors obesity and gender. The third GLM implemented a multiple regression analysis including obesity and gender to investigate possible obesity- and gender-associated differences in PE coding within a priori defined masks of dorsal and ventral striatum. Finally, we entered individual contrast images obtained from the PPI analyses into a multiple regression model to assess obesity- and gender-associated differences in PE-related connectivity of ventral striatum.

We used a significance threshold of $p < .05$ corrected for multiple comparisons [family wise error (FWE) correction] on the cluster level for all fMRI analyses. Following our behavioral analyses, all fMRI related models included impulsivity as a covariate and age as a nuisance variable to account for related effects. Anatomic labeling was performed with the help of AAL software [xjView toolbox (WFU Pickatlas), SPM8].

3. Results

3.1. Task performance

Both lean (n = 30) and obese (n = 28) subjects performed the task successfully, gradually improving prediction accuracy

over the four task blocks of 50 trials each [$F(3,156) = 103.41$, $p = 6.37*10^{-37}$; Fig. 1B]. RTs continuously decreased over the course of the experiment [$F(3,156) = 7.46$, $p = .0001$; Fig. 1E]. Obese subjects exhibited a lower learning performance over the entire task compared with lean participants (Table 3; Fig. 1B). This performance difference started to evolve between trial 30 and 40 (Fig. 1C). Obese subjects also responded faster throughout the experiment (Table 3; Fig. 1E) and less consistent than lean subjects (Table 3).

3.2. Strategy use

Over the course of the experiment, subjects gradually learned to integrate information from multiple cues to form predictions [$F(3,156) = 23.44$, $p = 1.41*10^{-12}$] and random-like choice behavior decreased across subjects [$F(3,156) = 20.82$, $p = 1.84*10^{-11}$]. Complementing the performance differences, lean subjects used significantly more often complex multi-cue strategies than obese participants [M ± SE: lean: 67.66 ± 4.05%; obese: 41.60 ± 5.58%; $F(1,52) = 16.03$, $p = .000021$]. This was not mirrored by an inverse relationship with respect to simpler single-cue strategies [M ± SE: lean: 20.67 ± 1.91%; obese: 24.41 ± 2.80%; $F(1,52) = 1.17$, $p = .28$]. Instead, obese participants' behavior was classified as random-like significantly more often than that of lean subjects [M ± SE: lean: 11.61 ± 3.04%; obese: 34.03 ± 5.10%; $F(1,52) = 16.56$, $p = .00002$]. This is in line with the observation of less consistent response behavior in obese compared with lean participants.

3.3. Prediction error utilization

In line with a reduced learning performance, obese compared with lean subjects showed higher absolute positive and negative PE amplitudes (Table 3) throughout the task, reflecting overall a larger discrepancy between the predicted and the actual outcomes. To infer whether obese subjects show deficits in behavioral adaptation related to a deficiency of using negative PEs for behavioral adjustment, we computed separate correlation analyses for positive and negative PEs with task performance in obese and lean participants. Task performance was highly correlated with both positive and negative PE amplitude in lean subjects ($n = 30$; positive PE: $R^2 = .79$, $p = 4.70*10^{-11}$; negative PE: $R^2 = .22$, $p = .009$, Fig. 2C, D). As expected, there was a large difference between the impact of positive and negative PEs on learning performance in obese participants. Only positive PEs ($n = 28$, $R^2 = .84$, $p = 7.06*10^{-12}$, Fig. 2E) had a significant impact on learning performance but not negative PEs ($n = 28$, $R^2 = .003$, $p = .78$, Fig. 2F). A rmANOVA revealed a significant interaction of obesity, PE sign and task performance [$F(1,54) = 6.67$, $p = .013$], showing that the insufficient utilization of PEs for behavioral adaptation is specific for negative PEs in obese subjects.

In addition, we analyzed modeled learning rates. Overall, subjects' learning rates were relatively small, reflecting the difficulty of the task due to its probabilistic nature, with higher learning rates related to positive PEs than learning rates associated with negative PEs [M ± SE: $\alpha^+ = .12 \pm .008$, $\alpha^- = .05 \pm .003$; $F(1,52) = 62,62$, $p = 1.75*10^{-10}$, Fig. 2A].

As hypothesized, obese subjects utilized negative PEs to a lower extent than lean subjects for subsequent behavioral adaptation, reflected by significantly smaller learning rates related to negative PEs in obese than lean subjects [$\alpha^-(l) = .06$, $\alpha^-(o) = .05$; $F(1,52) = 8.03$, $p = .007$, Fig. 2A]. In contrast, we found no obesity-related difference in learning rates related to positive PEs [$\alpha^+(l) = .12$, $\alpha^+(o) = .12$; $F(1,52) = .27$, $p = .61$, Fig. 2A]. However, a rmANOVA testing the interaction between feedback-specific learning rates and obesity did not reach significance [$F(1,52) = 2.22$, $p = .14$].

Subjects' response consistencies, reflected by the model's consistency parameter, were significantly lower for obese compared with lean subjects [$\beta(l) = 2.57$, $\beta(o) = 1.87$; $F(1,52) = 10.44$, $p = .002$]. Importantly, individually fitted response consistencies strongly correlated with subjects' individual switch rates ($n = 58$, $R^2 = .9$, $p = 1.29*10^{-29}$, Fig. 2B), demonstrating the temperature parameter β to be a meaningful model for subjects' response behavior with an adequate fit.

3.4. Neural correlates of prediction formation

We first assessed general BOLD activation patterns during stimulus-onset of WPT trials compared with motor-baseline trials. At this time-point, subjects perceive the predictive stimulus pattern, perform memory retrieval of former stimulus-response associations, and based on this, generate predictions about the correct association. For the sake of simplicity, we label this 'prediction formation' in the remainder of the manuscript. In line with previous findings (Poldrack et al., 2001, Poldrack and Rodriguez, 2004), prediction formation was associated with increased BOLD activation in striatum (caudate nucleus, putamen), anterior insula, inferior and middle frontal gyrus (BA 9, 46), supplementary motor area (BA 6, 32) and dorsal anterior cingulate cortex (BA 32), inferior parietal lobe (BA 40), precuneus (BA 7), as well as parts of visual (BA 17, 23) and motor cortex (BA 6). A decreased BOLD signal during prediction formation was observed in parts of the default mode network, i.e., medial prefrontal cortex, extending from superior frontal gyrus (BA 9) to medial frontal gyrus (BA 10), inferior parietal lobe (BA 40), as well as middle cingulate gyrus (BA 31), superior temporal gyrus, and

Table 3 – Behavioral and modeling data.

	Normal weight	Obese	F-value	p-value
Prediction accuracy [% correct]	73.28 ± 1.59	64.71 ± 1.88	$F(1,52) = 8.49$	$p = .006$
Reaction Time [sec]	1.57 ± .05 sec	1.44 ± .04 sec	$F(1,52) = 5.05$	$p = .039$
Response switches [%]	25.79 ± .02%	34.37 ± .02%	$F(1,52) = 13.89$	$p = .000048$
Absolute PE amplitude	.29 ± .006	.32 ± .007	$F(1,52) = 11.15$	$p = .002$

Notes: PE – prediction error. All values are given as mean and standard error.

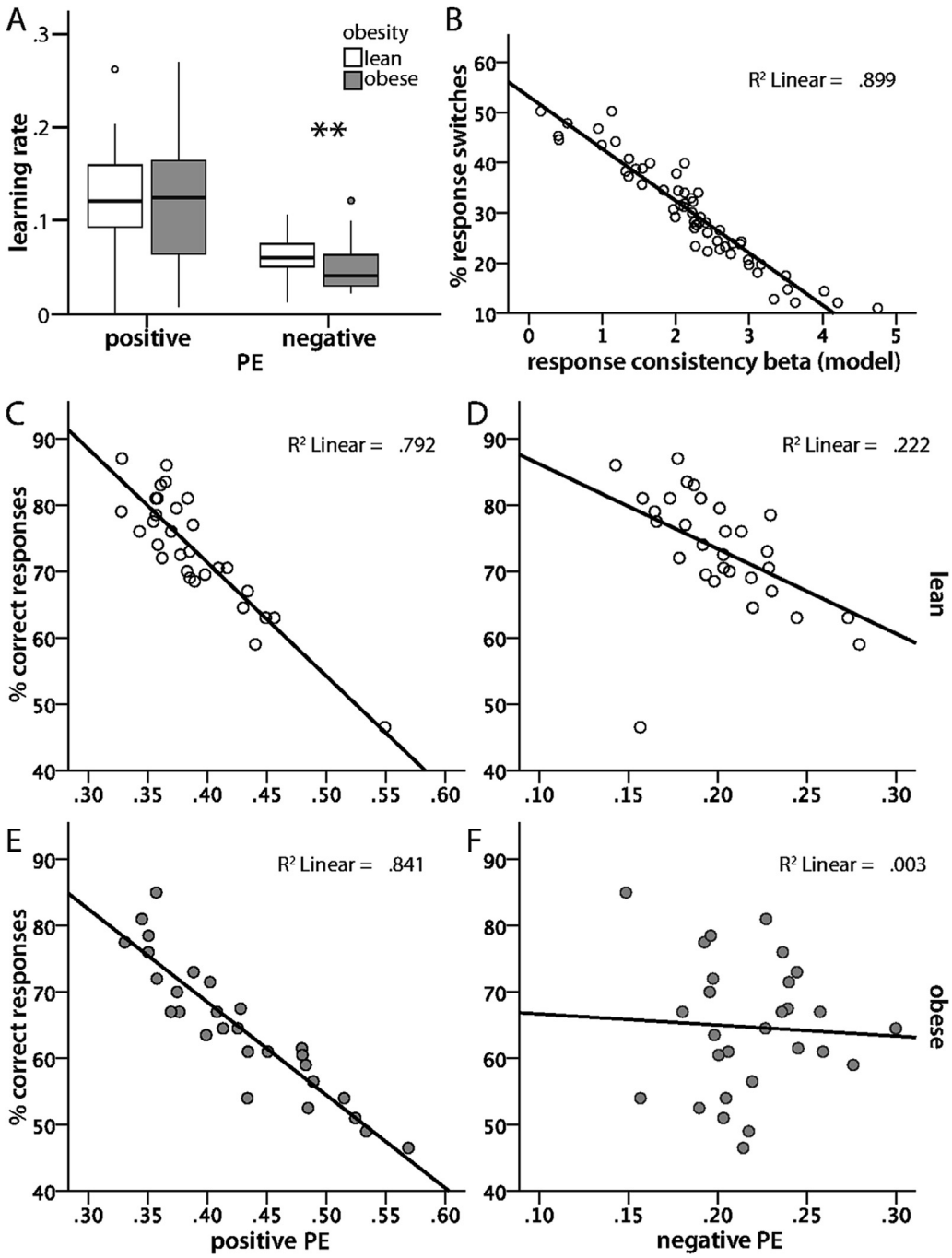

Fig. 2 – A) Obese (28) compared with lean subjects (30) reveal lower learning rates related to learning from negative PEs, whereas they show no differences in learning from positive PEs. Asterisks indicate statistical significance ($p < .01$). B) Modeled response consistency β correlated strongly with observed fraction of response switches (n = 58). C) Average strength of negative PEs and D) positive PEs correlated with learning performance of lean participants (30). E) In obese subjects (28) only average strength of positive PEs was associated with subjects' prediction accuracy, F) but not strength of negative PEs.

parahippocampus (BA 37) (Fig. 3A). Obese participants showed lower prediction-related BOLD activation in left superior frontal gyrus, left ventrolateral prefrontal cortex, bilateral precuneus and right premotor cortex than lean subjects (Table 4, Fig. 3B). We did not observe activation differences with respect to the opposite contrast (obese > lean).

3.5. *Neural correlates of stimulus complexity*

The capability to integrate predictive information from several cues in more complex stimulus patterns is also of importance for successful task performance. Therefore, we analyzed cortical and subcortical activation related to stimulus

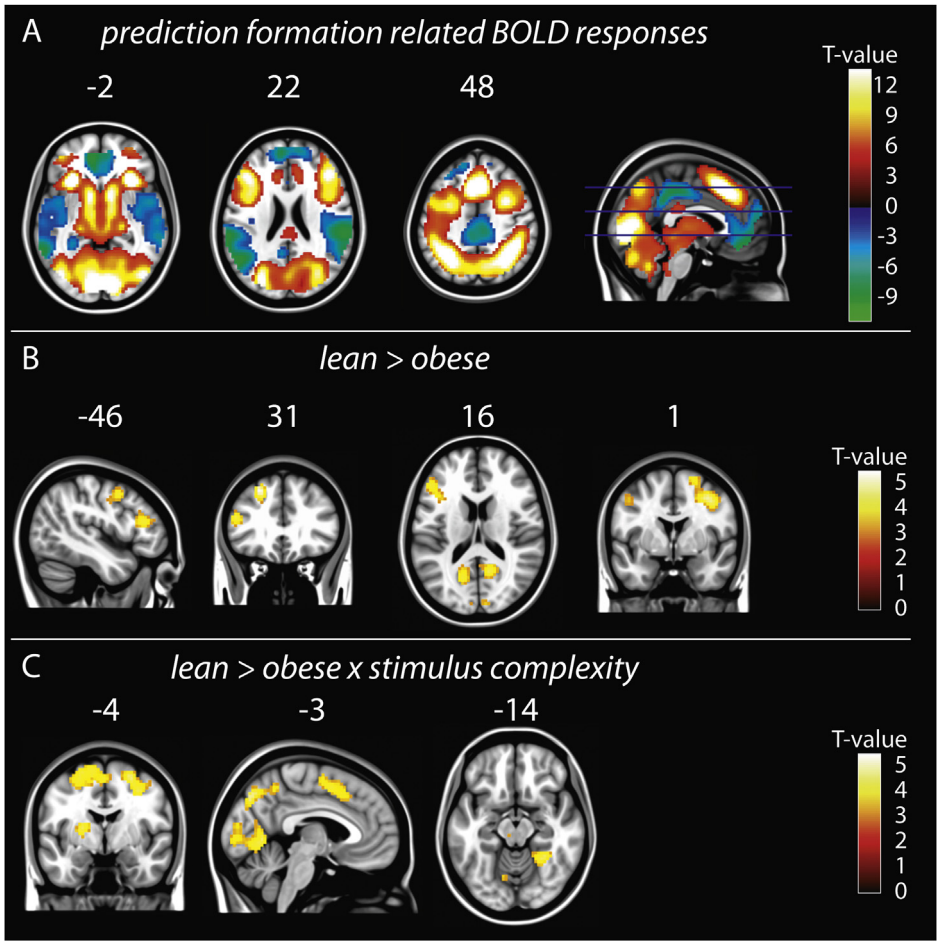

Fig. 3 – A) Regions in red-to-yellow color showed significantly higher prediction formation related BOLD activation than motor-baseline activation, whereas regions that demonstrated relatively lower BOLD activity are coded in blue-to-green color (n = 58). B) Lean subjects (30) revealed higher prediction-related BOLD activation in ventrolateral PFC, SFG, precuneus and premotor cortex than obese subjects (n = 28). C) Lean subjects (30) recruited left dorsal striatum, dACC, right parahippocampus and parts of motor cortex, precuneus, and lingual gyrus more strongly with increasing stimulus complexity than obese subjects (28).

complexity, i.e., to the number of cues presented in each trial. Increasing stimulus complexity was associated with increasing BOLD signal in premotor cortex, supplementary motor area, dorsal anterior cingulate, dorsal striatum, thalamus, anterior insula, precuneus, as well as in parts of the visual cortex (BA 17–19). Lean participants exhibited stronger complexity-related increases in BOLD activation than obese in left putamen, premotor cortex, supplementary motor area extending into dorsal anterior cingulate, right thalamus, precuneus, lingual gyrus extending into right parahippocampus and left inferior parietal lobe than obese subjects (Fig. 3C, Table 4).

3.6. *Neural correlates of prediction error utilization*

PE signals are assumed to be reflected in PE-related modulation of BOLD activation within ventral striatum (D'Ardenne et al., 2008; McClure et al., 2003; O'Doherty et al., 2003; Pessiglione et al., 2006). Diminished utilization of negative PEs to guide efficient behavioral adaptation may either result from 1) insufficient PE coding within striatal dopaminergic target regions or from 2) inadequate transmission of PE signals to higher cortical areas involved in modification of response behavior. To test if obese subjects show general alterations in PE signal coding within striatum we conducted a regression analysis based on subject-specific, trial-wise positive and negative PEs, a priori masked for ventral and dorsal striatum. Trial-specific signed PE values positively correlated with BOLD activation within ventral and dorsal striatum (Table 5, Fig. 4A) in accordance with (D'Ardenne et al., 2008; McClure et al., 2003; O'Doherty et al., 2003; Pessiglione et al., 2006). We observed no significant differences between lean and obese participants. Thus, obese subjects do not show alterations in PE coding within striatal target regions.

However, individuals with obesity showed attenuated learning from negative PEs ($\hat{\alpha}-$) compared with lean subjects. Therefore, we further assessed obesity-related alterations in PE-modulated functional coupling as a marker of a lower utilization of negative PEs to guide behavioral adaptation. We computed a PE-related PPI analysis (Park et al., 2010) with ventral striatum as seed region. Group comparisons revealed that obese subjects showed weaker functional coupling between ventral striatum and supplementary motor area (SMA)

Table 4 – BOLD activation peaks – prediction formation & stimulus-complexity.

	MNI-Coordinates (peak voxel)	# voxels	Z-Score	*p*-value
(1) Obesity × prediction formation				
Left superior frontal gyrus (BA 8)	−21, 35, 43	175	5.03	.007
Left ventrolateral PFC (BA 46)	−48, 32, 19	231	4.13	.002
Bilateral precuneus (BA 7, 31)	12, −58, 19	873	4.49	.000
Right premotor cortex (BA 6)	36, −1, 46	227	4.58	.002
(2) Obesity × stimulus-complexity				
Left putamen	−21, −4, 10	158	4.03	.004
Supplementary motor area (BA 6)	−18, −7, 64	490	4.02	.000
Extending into:	0, 14, 46	–	3.99	
- Bilateral dACC (BA 32)				
Right premotor cortex (BA 6)	24, −1, 61	197	4.57	.001
Right thalamus	15, −16, 1	143	4.13	.007
Bilateral precuneus (BA 7, 31)	−6, −73, 46	555	4.59	.000
Lingual gyrus (BA 18)	6, −82, 1	737	4.23	.000
Extending into:	30, −46, −14	–	4.07	
- Right parahippocampus (BA 37)				
Left inferior parietal lobe (BA 40)	−36, −37, 40	140	3.93	.007

Notes: (1) BOLD activation peaks of brain regions that were more strongly activated in lean subjects than in obese subjects during prediction formation. (2) Brain areas that were more strongly recruited in lean than in obese subjects with increasing stimulus complexity (all FWE-corrected on cluster level with $p < .05$).

(Z = 4.40, $p = .005$) as well as motor cortex (MC) (Z = 3.97, $p = .035$) than lean participants (Table 5). In agreement with our behavioral observations, post-hoc analysis showed that differences in ventral striatal functional connectivity were predominantly accounted for by negative PEs (Table 5, Fig. 4B). A rmANOVA revealed a significant interaction of obesity and PE sign regarding strength of functional coupling subsequent to PEs within SMA (Z = 3.85, $p < .05$, Table 5). This supports our hypothesis that the obesity-related attenuation of utilizing PEs to adequately adapt behavior is specific to negative PEs. Strength of functional coupling between ventral striatum and SMA associated with negative PEs was predictive of subjects' learning performances (n = 58, $R^2 = .1$, $p = .016$, Fig. 4C). Notably, strength of functional connectivity also predicted subjects' efficiency of utilizing negative PEs for behavioral adaptation, as reflected by its association with modeled learning rates from negative PEs ($\hat{\alpha}-$) (n = 58, $R^2 = .12$, $p = .007$, Fig. 4D). Obese compared with lean subjects did not show brain regions with greater PE-related functional connectivity with ventral striatum.

Table 5 – BOLD activation peaks – PE coding and related functional connectivity differences as assessed by PPI analysis.

	MNI-Coordinates (peak voxel)	# voxels	Z-Score	*p*-value
(1) PE coding				
Left dorsal striatum	−30, −13, 7	363	5.90	.000
	−9, 20, −8	–	4.09	
Extending into:				
- Left ventral striatum				
Right dorsal striatum	33, −10, 7	350	5.63	.000
	6, 17, −5	–	3.76	
Extending into:				
- Right ventral striatum				
(2) PPI – ventral striatum, l > o				
Left SMA	−12, −4, 61	136	4.40	.005
Left MC	−42, −25, 46	84	3.97	.035
(3) PPI – ventral striatum, l > o				
Negative PEs				
Left SMA	−12, −1, 61	131	5.30	.000
Left MC	−42, −25, 43	80	4.28	.000
(4) PPI – ventral striatum, l > o				
Positive PEs				
Left SMA	−9, −4, 58	3	3.22	.036
(5) PPI – ventral striatum, PE-type × obesity				
Left SMA	−12, −1, 61	6	3.85	.025

Notes: (1) PE coding related peaks of BOLD activation within ROIs of ventral and dorsal striatum. (2) Lean subjects showed greater PE modulated functional coupling between ventral striatum and SMA and MC than obese participants. (3) Differences in functional connectivity were accounted for by negative PEs, (4) but not positive PEs. (5) A significant interaction of PE-type and obesity revealed that the attenuated functional connectivity in obese subjects is related to negative PEs in particular.

3.7. *Influence of gender and trait impulsivity*

To ensure that our obesity-related findings are not accounted for by impulsivity or gender, we considered trait impulsivity as assessed by the Barratt Impulsiveness Scale and gender as modulating factors in our analyses. Importantly, trait impulsivity did not differ between groups of lean and obese participants (Table 1). We did not find significant effects of gender with respect to our behavioral as well as fMRI analyses. Across subjects, trait impulsivity was negatively associated with WPT performance [F(1,52) = 4.71, $p = .035$] and positively correlated with the number of switches between responses [F(1,52) = 5.42, $p = .024$]. In line, trait impulsivity was negatively correlated with modeled subject-specific response consistency [F(1,52) = 4.95, $p = .03$], average learning rate [F(1,52) = 4.4, $p = .04$] and averaged PE amplitude [F(1,52) = 9.58, $p = .003$], derived from the computational model. Moreover, independent of the factors obesity and gender, higher impulsivity was associated with a higher degree of random-like choices [F(1,52) = 7.79, $p = .007$] and with a lower number of multi-cue strategies subjects used to solve

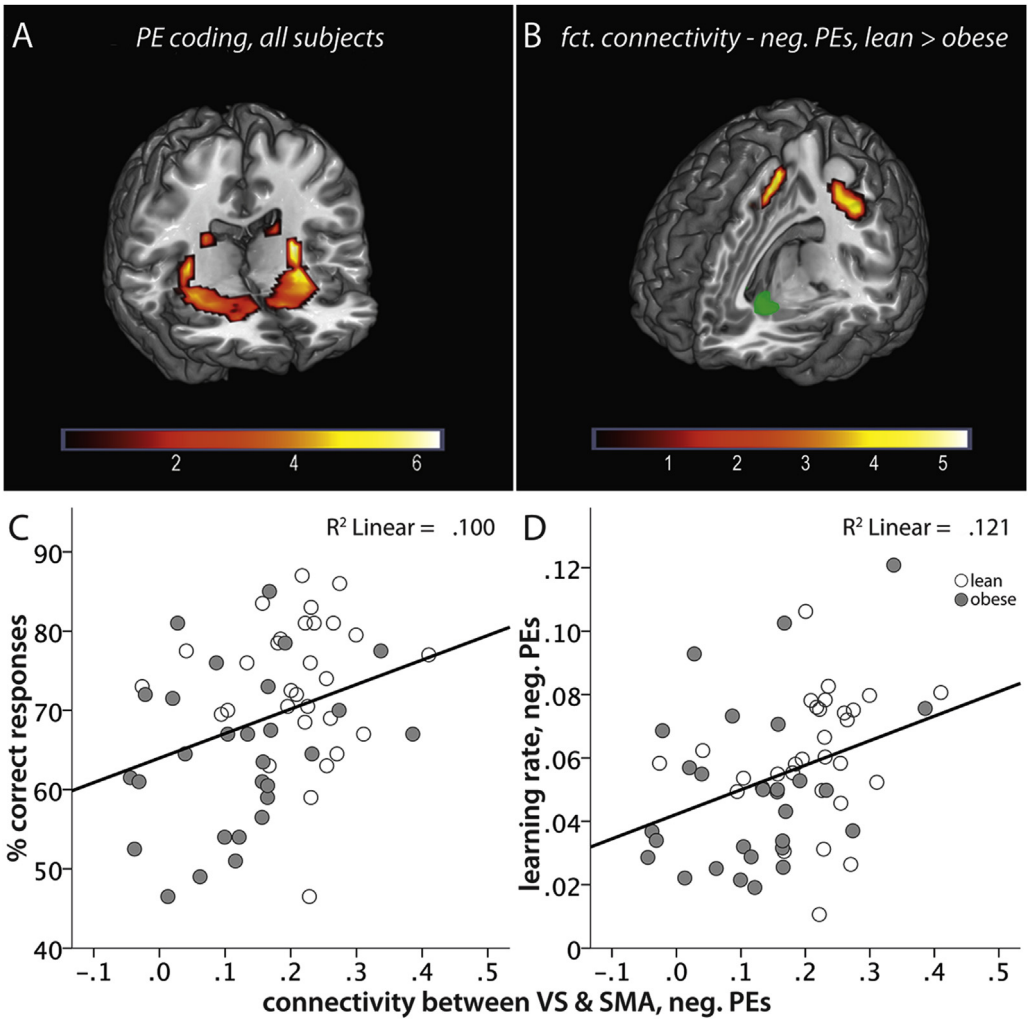

Fig. 4 – A) PE-related BOLD activation within ventral and dorsal striatum (n = 58). B) Obesity-related differences in negative PE-modulated functional connectivity (PPI) between ventral striatal seed region (green) and supplementary motor area (SMA) and motor cortex. C) Strength of functional coupling subsequent to negative PEs between ventral striatum (VS) and SMA significantly correlated with learning performance and D) predicted subjects' efficiency of utilizing negative PEs for behavioral adaptation (n = 58).

the task [F(1,52) = 5.22, p = .026]. We did not find any modulatory effect of impulsivity on obesity-related differences. Neither did we observe any association of impulsivity and BOLD activation within our analyses.

4. Discussion

4.1. *Summary*

Our data provide evidence for reduced utilization of negative PEs in the guidance of behavior in obesity in a non-food context. This was mirrored on the neural level by an obesity-associated reduced functional coupling between ventral striatum and SMA specifically following negative PEs. Strength of functional coupling was predictive of task performance measures. Throughout the task, obese compared with lean subjects exhibited less consistent response behavior and a reduced implicit learning performance.

4.2. *Inefficient utilization of negative PEs*

In line with previous findings of difficulties in negative outcome learning in individuals with obesity (Coppin et al., 2014), our behavioral results point at an insufficiency in using negative PEs to update predictions and translating these into behavioral adaptation. This implicates the involvement of the indirect dopaminergic pathway, since learning from negative feedback is supposed to rely on dips in dopamine transmission that modulate plasticity through D2 receptors (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007). It has been shown previously for different tasks including the WPT that learning from negative outcomes depends in an inverted u-shape manner on baseline binding potential of D2 receptors and that changes in DA tone affect predominantly learning from negative prediction errors (Cox et al., 2015; Floresco, 2013; Mathar et al., 2017). Further, individuals with genetically decreased number of D2 receptors show marked impairments in learning from negative outcomes (Klein et al.,

2007). For moderately obese subjects, it has been proposed that markers of obesity might either be associated with a heightened availability of D2 receptors (Dunn et al., 2012; Guo et al., 2014) or with a reduction in dopaminergic tone, resulting in a heightened measured availability of D2 receptors (Horstmann, Fenske, et al., 2015). Thus, our data support both interpretations, namely an increase in D2 receptors or a decreased DA tone in individuals with moderate obesity. It has been observed that neural activity reflecting anticipation of a predicted rewarding outcome associated with food (i.e., cue-induced reactivity) was considerably larger in obese than in lean subjects (Boswell & Kober, 2015; Murdaugh, Cox, Cook, & Weller, 2012; Nummenmaa et al., 2012; Sun et al., 2015; Verdejo-Román et al., 2016), but brain responses upon receipt of a rewarding food outcome were diminished (Frank et al., 2012; Stice, Spoor, Bohon, Veldhuizen, & Small, 2008b). Thus, one may hypothesize that in obese individuals negative PEs regarding food reward do not lead to appropriate down-scaling of anticipatory responses and consecutive adaptation of eating behavior, comparable to addictions to drugs of abuse (Heinz et al., 2004; Keiflin & Janak, 2015; Koob & Volkow, 2016; Park et al., 2010; Volkow, Wang, Fowler, Tomasi, & Telang, 2011).

Functional connectivity analysis revealed a reduced negative PE-related functional coupling between ventral striatum and SMA as well as MC. Alterations in D2 receptor based synaptic plasticity during learning driven by negative PEs might diminish functional coupling between striatum and its projection sites such as SMA and MC. Within cortico-striatal loops (Haber & Knutson, 2010), SMA has been implicated in retroactive adaptation of behavior (Chen, Scangos, & Stuphorn, 2010; Narayanan, Cavanagh, Frank, & Laubach, 2013), i.e., modification of responses based on preceding error feedback. These error-related signals are then relayed to MC (Narayanan et al., 2013). Importantly, in SMA we observed differences between lean and obese groups during two distinct time periods of the trial: During stimulus onset, where we observed differences associated with stimulus complexity, and during feedback onset, where we observed differences in coupling between ventral striatum and SMA during processing of negative PEs. Thus, the observed obesity-associated activation differences within SMA are presumably associated with distinct neural processes: During stimulus onset, SMA activity most probably reflects stimulus processing, prediction formation of cue-outcome associations, and stimulus-response mapping (Ariani, Wurm, & Lingnau, 2015; Hoshi & Tanji, 2007) while during feedback presentation SMA activity reflects feedback-related adaptation of cue-outcome associations (Chen et al., 2010; Narayanan et al., 2013).

4.3. *Attenuated fronto-striatal BOLD activation*

We found marked functional activation differences between lean and obese subjects within the fronto-striatal circuitry, in parahippocampus and precuneus. The latter regions have previously been implicated in encoding and retrieval processes during classification learning (Moody, Bookheimer, Vanek, & Knowlton, 2004; Poldrack et al., 2001). Interestingly, they are also involved in signaling satiation (Lohmann et al., 2010) and have been linked to related alterations in obesity (Gautier et al., 2000; Kullmann et al., 2011; Parigi et al., 2002). Our results provide evidence that these obesity-related alterations generalize to a non-food specific context. Further, obese compared to lean subjects revealed decreased prediction-related BOLD activation in PFC. Within PFC, dopamine is supposed to support learning through stabilization of stimulus representations via D1 receptor transmission, and flexible updating processes mediated by D2 transmission (Cools & D'Esposito, 2011; Durstewitz & Seamans, 2008). Accordingly, the balance between D1 and D2 transmission in PFC is believed to crucially determine learning performance (Durstewitz & Seamans, 2008; O'Reilly, 2006), which furthermore depends on tonic dopamine concentration in an inverted U-shaped fashion (Cools & D'Esposito, 2011). Recent findings in rodents have associated obesity with heightened tonic dopamine levels combined with decreased phasic signaling (Narayanaswami, Thompson, Cassis, Bardo, & Dwoskin, 2013). For humans, a dynamic relationship between DA tone and markers of obesity has been proposed (Horstmann, Fenske, et al., 2015). Thus, an imbalance in prefrontal dopamine transmission might cause the observed higher inconsistency in response behavior and related lower learning performance in our obese subjects. Further, impulsivity correlated with the inconsistency of response behavior. This is in line with inappropriate attention to irrelevant information, a key characteristic of impulsivity, and with the observation that impulsivity is related to lateral PFC function and dopaminergic transmission (Aron, Dowson, Sahakian, & Robbins, 2003; Congdon, Constable, Lesch, & Canli, 2009; Cummins et al., 2011). However, the contribution of different facets of impulsivity to the development and maintenance of obesity is currently hotly debated. While some aspects, e.g., temporal impulsivity, seem to be reliably associated with obesity (Amlung, Petker, Jackson, Balodis, & MacKillop, 2016; McClelland, Dalton, Kekic, Bartholdy, Campbell, & Schmidt, 2016; Simmank, Murawski, Bode, & Horstmann, 2015), others are not (Dietrich, Federbusch, Grellmann, Villringer, & Horstmann, 2014).

Converging evidence points at a relationship between obesity and brain structure and function in cognitive control-related frontal cortices (Horstmann et al., 2011; Volkow et al., 2009). To date, most studies assessing fronto-striatal functioning in obesity focused on food processing (Martens et al., 2013; Stice et al., 2008b) despite the well-known involvement of these pathways in fundamental processes like feedback learning. Our results contribute to the emerging understanding that the observed differences in obesity extend to more general cognitive functions beyond the food context (Dagher, 2012; Coppin et al., 2014; Gonzales et al., 2010; Vainik, Dagher, Dubé, & Fellows, 2014; Verdejo-García et al., 2010).

4.4. *Limitations*

Although we discuss an imbalance between tonic and phasic dopamine transmission as a possible underlying mechanism of the observed effects, this conclusion is based on literature findings on the relation between DA and obesity in humans and rodents. To directly relate our observations to differences in dopaminergic transmission, direct assessment via Positron Emission Tomography (PET) or pharmacological modulation during learning the WPT would be necessary.

As this study is cross-sectional, we cannot infer whether the observed effects are cause or consequence of obesity. In rodents, there is ample evidence that diet induced obesity or dietary intake of fat and sugar impacts on the efficacy of dopaminergic transmission (Alsiö et al., 2010; Cansell et al., 2014; Cone, Chartoff, Potter, Ebner, & Roitman, 2013, 2014; Furlong, Jayaweera, Balleine, & Corbit, 2014; Geiger et al., 2009; Johnson & Kenny, 2010; Narayanaswami et al., 2013; van de Giessen et al., 2013, 2012). These data would imply that differences in the dopaminergic system are secondary to dietary factors, an increase in adiposity, or both. In line, Friend et al. (2017) revealed in mice that deficits in striatal dopamine D2 receptor binding are a consequence of diet-induced obesity and that removing D2 receptors did not lead to a higher prevalence of obesity. However, the picture is further complicated by (a) metabolic changes during the development of obesity, e.g., impacting on the level or dynamic responses of hormones such as ghrelin, leptin, and insulin, which are in turn affecting central dopaminergic transmission (Cone et al., 2014; Fulton et al., 2006), and (b) genetic factors affecting dopaminergic transmission that seem to be associated with the risk for weight gain and brain responses to reward (Davis et al., 2008; Stice, Spoor, Bohon, & Small, 2008a; Yokum, Marti, Smolen, & Stice, 2015) but not obesity *per se* (Benton & Young, 2016). In the light of this complexity, a model is favored at present that postulates an interaction between an initial vulnerability defined by genetic factors, and subsequent changes induced by metabolic and dietary effects to explain the link between dopaminergic transmission, eating behavior and obesity.

5. Conclusion

In summary, we demonstrated obesity-related differences in PE-guided behavioral adaptation and fronto-striatal functioning in the absence of food-related stimuli. Future work should focus on longitudinal studies to reveal if the here found alterations are a consequence of overeating or possibly predispose to excess weight. Our results are highly relevant for understanding obesity-associated general alterations in behavior and brain function and for the development of new and non-invasive therapeutic strategies in the future. These could e.g., comprise approaches such as pharmacotherapy or focused ultrasound of dopaminergic source regions to target the possibly different tonic DA levels within the striatum of obese subjects.

Author contributions & funding

DM, JN and AH designed research. DM and JN implemented computational model, DM analyzed data, DM, JN and AH wrote paper. All authors revised and edited the manuscript.

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ORIGINAL RESEARCH
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Is it Worth the Effort? Novel Insights into Obesity-Associated Alterations in Cost-Benefit Decision-Making

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Cost-benefit decision-making entails the process of evaluating potential actions according to the trade-off between the expected reward (benefit) and the anticipated effort (costs). Recent research revealed that dopaminergic transmission within the fronto-striatal circuitry strongly modulates cost-benefit decision-making. Alterations within the dopaminergic fronto-striatal system have been associated with obesity, but little is known about cost-benefit decision-making differences in obese compared with lean individuals. With a newly developed experimental task we investigate obesity-associated alterations in cost-benefit decision-making, utilizing physical effort by handgrip-force exertion and both food and non-food rewards. We relate our behavioral findings to alterations in local gray matter volume assessed by structural MRI. Obese compared with lean subjects were less willing to engage in physical effort in particular for high-caloric sweet snack food. Further, self-reported body dissatisfaction negatively correlated with the willingness to invest effort for sweet snacks in obese men. On a structural level, obesity was associated with reductions in gray matter volume in bilateral prefrontal cortex. Nucleus accumbens volume positively correlated with task induced implicit food craving. Our results challenge the common notion that obese individuals are willing to work harder to obtain high-caloric food and emphasize the need for further exploration of the underlying neural mechanisms regarding cost-benefit decision-making differences in obesity.

Keywords: obesity, cost-benefit decision-making, physical effort, reward, voxel-based morphometry

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INTRODUCTION

Everyday decisions are guided by cost-benefit analyses. For example, whether or not we choose to walk to the next store to buy chocolate depends not only on how much we like chocolate and on our present state of hunger, but also on our subjective perception of the distance to the next store. Thus, we weigh the expected rewards an action will deliver against the effort for obtaining them to calculate a subjective utility value that guides our decisions.

Several studies have revealed that perceived effort strongly impacts on our decisions and that the fronto-striatal pathway is critical for integrating effort costs to form a decision in both animals and humans (Salamone et al., 1994; Bautista et al., 2001; Walton et al., 2002, 2006; Croxson et al., 2009; Basten et al., 2010). Mesolimbic dopamine was shown to play a key

role in the motivation to overcome costs in order to receive rewards (Salamone et al., 1994, 2007; Kurniawan et al., 2011; Salamone and Correa, 2012; Treadway et al., 2012). In particular nucleus accumbens (NAcc) dopamine is believed to modulate motivational salience in goal-directed behavior (Salamone and Correa, 2012).

In the case of obesity, identifying possible alterations in cost-benefit decision-making is of particular importance. In our obesogenic environment potent food is always available at minimal costs, and excess weight is associated with a reduced motivation for physical activity (Ness et al., 2007) and a possibly heightened valuation of potent food rewards (e.g., Rothemund et al., 2007).

Obesity has been characterized by a reduced binding potential of striatal dopamine receptors (Wang et al., 2001; de Weijer et al., 2011). This is hypothesized to be associated with a heightened striatal dopaminergic tone (Horstmann et al., 2015b). Further, obese individuals show a heightened neural activation during the anticipation of high-caloric food stimuli in dopaminergic target regions such as NAcc in the context of reward processing (e.g., Stice et al., 2008; Nummenmaa et al., 2012). This food-related hyper-responsiveness may point at a context-sensitive dopaminergic reward system, possibly mediated through food-related memory input from the ventral subiculum of the hippocampus (Belujon and Grace, 2011).

To date, only few studies have explored obesity-associated alterations in cost-benefit decision-making in humans. Two studies indicate that obese subjects may be willing to invest more effort to obtain high-caloric food than lean individuals (Epstein et al., 2007; Giesen et al., 2010). Both studies used button presses as a measure of physical effort and assessed obesity-associated alterations in cost-benefit decisions solely with respect to food reward. It is thus not clear if the results generalize to other reward categories. Further, findings in rodents related to cost-benefit decision-making in obesity are mixed, with some studies showing a heightened willingness to work for food rewards in diet-induced obese animals (e.g., Narayanaswami et al., 2013) and others revealing the opposite (e.g., Harb and Almeida, 2014).

Thus, there is need for a systematic investigation of cost-benefit decision-making in obesity that involves properly demanding physical effort measures and food and non-food reward categories.

Importantly, cost-benefit decision-making, with its strong reliance on dopaminergic pathways, may be modulated by a multitude of factors, in addition to obesity. Hence, a thorough investigation of obesity-associated cost-benefit decision making necessitates the inclusion of possible confounding factors. Gender has been revealed to alter dopaminergic neurotransmission, and recently estradiol was shown to modulate dopamine baseline dependent cognitive functioning in humans (Haaxma et al., 2007; Jacobs and D'Esposito, 2011) and cost-benefit decision-making in rodents (Uban et al., 2012). Further, gender has been shown to modulate obesity-related differences in brain structure and related processes of cognitive control (Horstmann et al., 2011). In the context of reinforcement sensitivity theory, reward and punishment sensitivity are both known to rely on dopaminergic activity (Maril et al., 2013; Tomer et al., 2014) and may impact sensitivity to rewards and effort demands in cost-benefit decisions. Further, both are associated with eating behavior (Loxton and Dawe, 2006; Matton et al., 2013; Dietrich et al., 2014). In the case of obesity, additional psychosocial factors, such as concerns about one's own body image, may modulate food-related cost-benefit decisions. Following findings regarding stigmata in obesity (e.g., Forste and Moore, 2012), one would for example expect self-reported body dissatisfaction to decrease motivation to invest effort for high-caloric food specifically in obese women. As a potent environmental factor affecting effort-based decision-making, stress was shown to modulate dopaminergic transmission within the fronto-striatal system (Nagano-Saito et al., 2013; Pruessner et al., 2013) and to reduce intrinsic motivation to invest effort in rodents (Shafiei et al., 2012). Stress has also been linked to eating behavior and body weight (Warne, 2009; Tomiyama et al., 2011).

In this study we investigate obesity-associated alterations in cost-benefit decision-making and in related reaction times regarding physical effort and different kinds of food and non-food rewards. We designed a novel cost-benefit decision-making paradigm in which subjects can choose to invest physical effort via a digital handgrip device to receive rewards out of three distinct categories: money, fruit and sweet high-caloric snacks. We hypothesize that obese compared with lean subjects show alterations in cost-benefit decision-making particularly in relation to high-caloric sweet snack food. We expect that gender and subjects' self-reported body dissatisfaction strongly modulate willingness to exert effort for sweet snacks in obese participants. Obese participants with high body dissatisfaction may be less driven to invest effort for high-caloric food reward compared with lean subjects. The impact of body dissatisfaction on subjects' cost-benefit decisions may be more prominent in women than in men. Further, we expect that perceived chronic stress level negatively correlates with subjects' motivation to invest effort. As physical effort may be experienced as a sort of punishment, high punishment sensitivity may reduce willingness to exert effort, whereas heightened reward sensitivity may enhance willingness to invest effort to receive rewards.

Beyond behavioral assessment, we apply voxel-based morphometry (VBM) in a subsample of our subjects. Based on recent findings (Schäfer et al., 2010; Horstmann et al., 2011), we hypothesize that obese compared with lean subjects show lower gray matter volume in cognitive-control related lateral prefrontal cortices (lPFC) and possibly higher gray matter volume in areas implicated in reward processing such as orbitofrontal cortex (OFC) and NAcc. We expect that volume of NAcc, as the dopaminergic core brain structure involved in the motivation to overcome costs to obtain rewards, positively correlates with subjects' willingness to exert effort. In addition, as NAcc activation has been related to craving severity (Kober et al., 2010) and its gray matter volume to eating behavior pathology and addiction-like behavior (Schäfer et al., 2010; Howell et al., 2013), we predict that NAcc gray matter volume positively correlates with task induced craving for high-caloric food.

MATERIALS AND METHODS

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 57 healthy Caucasian participants who were separated into four groups according to their BMI and gender: two obese (BMI $\geq$ 30, BMI $<$ 40) groups with 14 female and 15 male participants, and two lean control groups (BMI $\geq$ 19, BMI $\leq$ 25), consisting of 15 female and 13 male subjects. The four groups were closely matched for educational background (i.e., years of scholastic education) and age distribution (**Table 1**). All participants were right-handed (Edinburgh Handedness Inventory, (Oldfield, 1971)), between 18 and 35 years old and reported to generally like fruits and sweets. Exclusion criteria were hypertension, dyslipidemia, metabolic syndrome, depression [Beck Depressions Inventar (BDI), Hautzinger, 1995 (german version of the Beck Depression Inventory (BDI-II), Beck et al., 1996; cut-off value 18; **Table 1**], a history of neuropsychiatric diseases, smoking, and diabetes mellitus type I and II. All subjects gave written informed consent before taking part in the study.

Stimuli

In our experiment, subjects could earn rewards from three distinct categories: money, fruit, and sweet snacks, and in two quantities: one or four pieces. Money was represented by two cent coins. Available fruit items included pieces of apple, banana, kiwi, nectarine, orange, pear, physalis, pineapple, raisins, and strawberries. Sweet snack items consisted of different small chocolate bars from Mars' celebration collection (Bounty, Dove, Dove-Caramel, Mars, Milkyway, Snickers, Teaser, Twix) and four different gummi bear-like snacks (Haribo Goldbären, Haribo Konfekt, Haribo Vampire, and Saure Apfelringe). During the task, reward stimuli were presented as photographs of the respective reward item that showed either one or four pieces, indicating the quantity of the reward item subjects could earn in the respective trial.

To earn the rewards during the task, subjects had to exert handgrip force. Force levels consisted of an easy and a hard category, with force levels drawn from two normal distributions with mean 50 or 67% and standard deviation 2% of subjects' individual maximum handgrip forces. A thermometer on the screen indicated the proposed level.

Before being instructed, subjects' maximum handgrip force was assessed with an isometric handgrip device (BIOPAC, TSD-121) to individually adjust effort levels in the subsequent task. To familiarize participants with the task, they performed 10 practice trials beforehand. During the task, subjects made their choices with a response pad in their left hand and exerted effort with the isometric handgrip device in their right hand. Subjects' right hand was videotaped to assure that subjects only gripped with their right hand during the task.

Visual Analog Scale (VAS) Rating and Questionnaires

Subjects were told to refrain from eating 3 h before the experiment when they were invited. When they entered the lab, subjects completed several questionnaires related to body dissatisfaction (EDI-2, Paul and Thiel, 2005; **Table 1**), reward and

TABLE 1 | Sample size, distribution of body mass index (BMI), age, years of education, depressive symptoms (BDI), punishment sensitivity (BIS), reward sensitivity (BAS), chronic stress level (TICS), self-reported body dissatisfaction, VAS hunger rating prior to experiment, task-induced implicit food craving, nine-point Likert Scale rating of subjects' wanting and liking of the individual sweet snack and fruit items that entered the task, subjects' maximum hand grip force, average reaction times and fraction of choices to exert effort throughout the task.

	Lean women	Obese women	Lean men	Obese men	*F-/H*-values	*p*
Sample size (sample size MRI)	15 (12)	14 (8)	13 (11)	15 (11)	–	–
BMI	22.1 ± 1.3	33.6 ± 2.0	21.4 ± 1.3	33.5 ± 2.6	$F_{(3, 53)} = 182.11$	**<0.001**
Age	24.3 ± 3.0	26.5 ± 4.5	26.1 ± 3.0	27.5 ± 3.6	$F_{(3, 53)} = 2.05$	0.12
Years of education	13 (13–13)	13 (10–13)	13 (13–13)	13 (10–13)	$H_{(3)} = 3.89$	0.27
BDI	2.7 ± 2.9	6.1 ± 5.1	3.5 ± 4.0	4.5 ± 4.5	$H_{(3)} = 3.90$	0.27
BIS	19.2 ± 2.5	18.8 ± 2.7	18.4 ± 3.3	17.7 ± 3.7	$F_{(3, 53)} = 0.67$	0.58
BAS	38.3 ± 9.3	37.9 ± 8.1	41.1 ± 4.9	37.6 ± 9.0	$F_{(3, 53)} = 0.48$	0.70
TICS	16.8 ± 7.5	18.4 ± 9.2	15.2 ± 7.1	16.9 ± 9.7	$F_{(3, 53)} = 0.30$	0.82
Body dissatisfaction	29.8 ± 10.3	44.1 ± 8.8	16.0 ± 5.3	38.5 ± 10.8	$F_{(3, 53)} = 22.62$	**<0.001**
Hunger prior to experiment	59.4 ± 22.7	56.2 ± 28.1	53.3 ± 20.7	58.6 ± 19.5	$F_{(3, 53)} = 0.02$	0.89
Implicit food craving	22.7 ± 18.3	32.4 ± 25.3	21.7 ± 20.3	17.6 ± 15.8	$F_{(3, 53)} = 1.43$	0.24
Wanting of included sweet items	7.7 ± 1.1	7.2 ± 1.0	7.5 ± 1.0	6.7 ± 1.4	$H_{(3)} = 5.82$	0.12
Wanting of included fruit items	8.1 ± 0.8	7.6 ± 1.1	7.9 ± 1.0	7.8 ± 0.8	$H_{(3)} = 2.39$	0.50
Liking of included sweet items	8.1 ± 0.9	7.3 ± 0.8	7.5 ± 0.9	7.1 ± 0.9	$H_{(3)} = 8.13$	**<0.05**
Liking of included fruit items	8.3 ± 0.7	7.8 ± 0.8	8.1 ± 1.0	8.2 ± 0.8	$H_{(3)} = 4.33$	0.23
Maximum grip force	27.1 ± 5.5	27.1 ± 5.6	43.1 ± 6.9	48.1 ± 9.2	$F_{(3, 53)} = 34.96$	**<0.001**
Reaction times	581.9 ± 74.1	672.3 ± 106.6	569.1 ± 62.9	614.2 ± 105.8	$F_{(3, 53)} = 3.63$	**<0.05**
% Choices of effort exertion	64.4 ± 15.0	65.4 ± 18.7	71.4 ± 17.0	56.6 ± 11.1	$F_{(3, 53)} = 2.17$	0.10

Values represent mean ± standard deviation, except for years of education [median (min max)]. Tests for group differences are based on Kruskal–Wallis–H-tests and ANOVA (F). Bold values represent significant group differences.

punishment sensitivity (German version of BIS/BAS scale, Carver and White, 1994; Strobel et al., 2001; **Table 1**), and chronic stress levels (TICS, Schulz et al., 2004; **Table 1**). Prior to performing the task, subjects were asked to rate how hungry they felt on a VAS (range: 0–100; 0, not hungry at all; 100, extremely hungry), to control for differences in hunger. After the task subjects were asked to rate their state of hunger again. We used the hunger difference before and after the task as an implicit measure of task-induced food craving.

Food Item Rating

To control for individual liking and wanting of the food items that entered the task, we assessed subjects' liking and wanting of the food items. Specifically, subjects were presented pictures of all food items on the computer screen in a randomized order and asked to rate them according to how much they liked the respective food. Subsequently, subjects were asked to rate the food items with respect to how much they wanted to eat the different food items right now. Liking and wanting ratings were obtained utilizing nine-point Likert scales, ranging from "not at all" (1) to "very much" (9). For each subject, the five "most wanted" sweet snacks and fruit items were chosen as stimuli in the subsequent cost-benefit task.

Task

In each trial of the task (**Figure 1A**), subjects were shown a picture of the available reward item (one or four pieces of the sweet snack, fruit, or money) and the required effort level they had to invest (high or low, indicated by a thermometer). In half of the trials, the order of reward and effort presentation was reversed. Subsequently, subjects decided whether they wanted to exert the effort level to receive the reward item or not. Subjects were instructed to decide as fast as possible. Reward and effort presentation each lasted for 1500 ms followed by a 2000 ms time interval where subjects had to indicate on a two button response pad in their left hand, whether they wanted to exert the respective

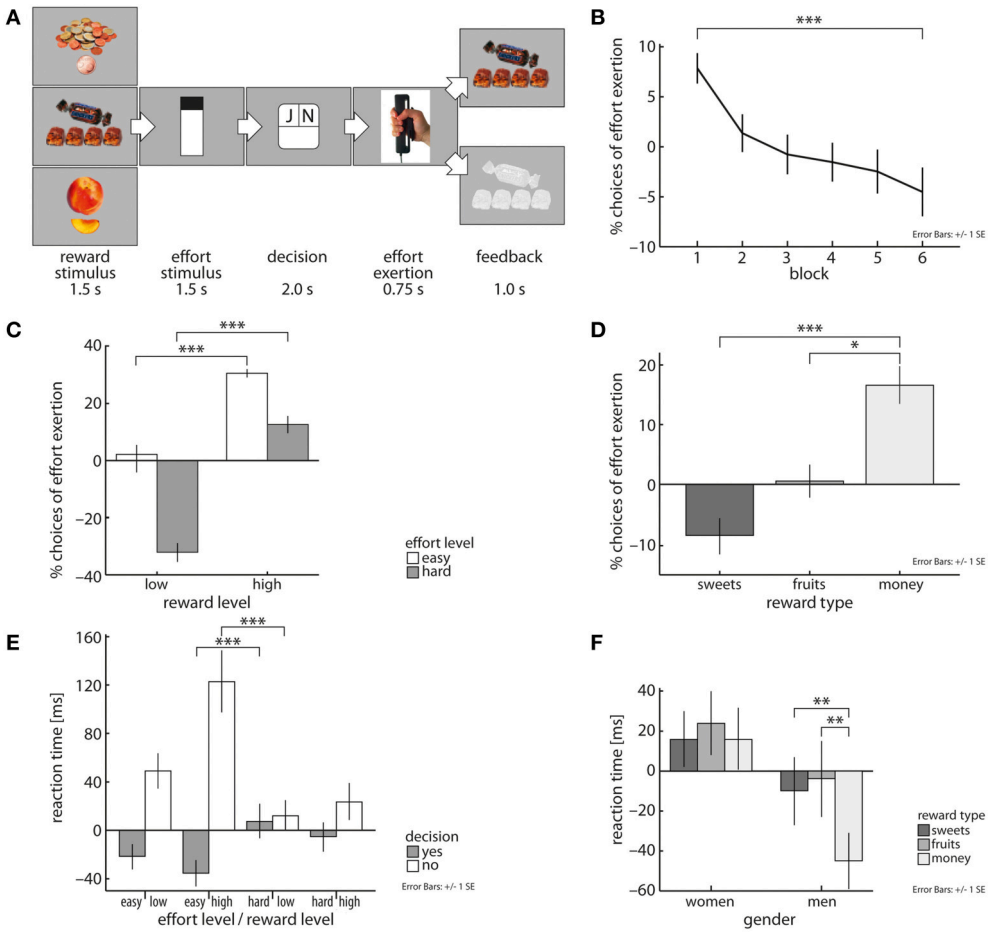

FIGURE 1 | Schematic representation of the novel cost-benefit decision-making task **(A)**. Across all subjects, likelihood of choosing to grip decreases over task blocks (40 trials each) **(B)** and is dependent on both effort and reward magnitude **(C)**. Subjects exerted effort more often for money than for fruit and sweet snacks **(D)**. Subjects decided fastest to expend effort in trials with low effort and high reward magnitudes and decided slowest to reject these offers **(E)**. Men decided faster in trials involving monetary reward than in food reward trials **(F)**. Depicted values are corrected for factors and covariates within the respective GEE model. Asterisks indicate significance within the respective GEE model reported in the Results Section.

effort level to receive the anticipated reward, or not. If they did not respond in time, a frowney appeared on the screen together with the instruction "too slow." Assignment of "yes" and "no" to the two response buttons was randomized over trials. After the decision, subjects either had to grip the required force level or passively waited for 2000 ms. If they chose to grip, subjects had to squeeze the hand grip device until the indicated level was reached on the thermometer within 2000 ms and had to maintain this force level for 750 ms. If subjects successfully finished the effort exertion phase, they received a positive feedback that consisted of a smiley and the earned reward displayed for 1000 ms. If they failed to do so or had chosen not to grip, they received negative feedback in the form of a frowney and a masked picture of the reward. The next trial started after an inter-trial-interval of 2000 ms. Reward category, reward and effort level and trial order (reward first/effort first) were randomized over the whole task and each block.

The task consisted of six blocks (lasting ∼10 min) composed of 40 trials each, leading to a total of 240 trials. Between trial blocks, subjects had 3 min time to relax their right hand from gripping. At the end of the task, subjects' maximum grip force was assessed again, to exclude that cost-benefit decisions were influenced by fatigue. Finally, subjects were paid a compensation of 7 €/h and received their earned sweet snacks, fruit pieces and additional reimbursement of up to 3 € according to their gained reward across money trials.

MRI Acquisition

We acquired T1-weighted images in a subsample of 42 [20 female, 19 (8 female) obese] participants on a whole-body 3T TIM Trio scanner (Siemens, Erlangen, Germany) with a 12-channel head-array coil using a MPRAGE sequence [TI = 650 ms; TR = 1300 ms; snapshot FLASH, TRA = 10 ms; TE = 3.93 ms; $\alpha = 10°$; bandwidth = 130 Hz/pixel (i.e., 67 kHz total); image matrix = 256 × 240; FOV = 256 × 240 mm; slab thickness = 192 mm; 128 partitions; 95% slice resolution; sagittal orientation; spatial resolution = 1 × 1 × 1.5 mm; two acquisitions].

Image Processing

Image pre-processing and statistical analysis were performed using SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm) running under MatLab 7.14 (Mathworks, Sherborn, MA, USA). MR images were processed using Diffeomorphic Anatomical RegisTration using Exponentiated Lie algebra (DARTEL) (Ashburner, 2007) with standard parameters for VBM. All analyses were performed on bias-corrected, segmented, registered (rigid-body transformation), interpolated isotropic (1.5 × 1.5 × 1.5 mm), and smoothed (FWHM 8 mm) images. All images were warped based on the transformation of the standard MNI152 DARTEL template to the GM prior image provided by SPM8 to meet the standard stereotactical space of the Montreal Neurological Institute (MNI). GM segments were non-linearly scaled by the Jacobian determinants of the deformations introduced by normalization to account for local compression and expansion during transformation.

Data Analysis

Behavioral Data

All analyses were performed with PASW-SPSS-Statistics 22.0 (IBM Corporation, Somers, NY, USA). A possible group-related difference with respect to subjects' VAS ratings of hunger was assessed by ANOVA. Differences in nine-point Likert scale liking and wanting ratings of individual food reward items that entered the task were assessed by Mann-Whitney U-tests. *Post-hoc* pairwise comparisons were computed with two sample *T*-tests or Mann-Whitney U-tests and adjusted for pairwise comparisons.

We applied a generalized estimating equations (GEE) approach to assess the impact of our variables of interest on subjects' reaction times and on subjects' single trial binary decisions. GEE is an extension of a generalized linear model that is capable of accounting for possible unknown correlations between residuals. An advantage of GEE is that its parameter estimates are consistent under mild regularity conditions, even when the covariance structure is mis-specified (Zeger and Liang, 1986). Computed GEE models utilized a first order autoregressive working correlation matrix, a linear normal outcome distribution for modeling reaction times and a binary logistic outcome distribution to model subjects' decisions to grip or not on each single trial, respectively.

We computed four successive GEE models for both reaction times and choice analysis, respectively. The first model contained as predictor variables trial block, trial order (reward first/effort first), reward category, reward and effort magnitude, and the interaction of the two latter. Based on our hypotheses we included obesity, gender, subjects' reward and punishment sensitivity, and perceived chronic stress as further predictors. To control for individual differences in wanting and possible effects of age, we included subjects' wanting ratings of the food items, and age as covariates. For analysis purposes, we set wanting ratings constantly to the highest value (9) for monetary reward, assuming that every participant wanted to receive money. As we wished to assess whether reaction times differed with respect to subjects' choices (yes/no), we also included the binary decision for each single trial and a three-way interaction term of effort magnitude, reward magnitude, and decision into the first GEE for reaction time analysis.

Covariates that yielded no statistical significance in the first GEE model, at least on a trend level ($p < 0.1$), were disregarded in subsequent GEE models. In the second GEE, we tested for obesity- and gender-specific two-way interactions, i.e., gender by effort magnitude, gender by reward category, obesity by effort level, obesity by reward category, and obesity by gender. The second model for choice analysis also included the interactions of obesity by trial block and gender by trial block to assess group-related differences over time. According to our hypotheses, the third GEE was set up to assess a three-way interaction of reward category, obesity, and gender. To test for a modulatory effect of body dissatisfaction, we assessed a four-way interaction between reward category, obesity, gender, and body dissatisfaction with the last GEE model.

Age, reward sensitivity, punishment sensitivity, chronic stress, and individual wanting ratings were mean centered prior to analyses. Self-reported body dissatisfaction was centered on the

respective group mean with regard to gender and obesity, as we were interested in its impact specifically for each group.

Post-hoc analyses of interaction effects were based on estimated marginal means (EMMs) of the mean response for reaction time analyses and on EMMs of the linear predictor of the binary outcome variable "decision" and consisted of Wald Chi-Square Tests and ANOVAs for pairwise comparisons, corrected for multiple comparisons utilizing Bonferroni correction.

Structural MRI Data

We utilized a full-factorial design within SPM8 running under Matlab 7.14 with factors obesity and gender, and fraction of yes decisions, wanting ratings (averaged over all sweet snack and fruit items), and implicit food craving (differences in hunger ratings post-pre) as covariates. Age and total intracranial volume were included to account for the confounding effects of age and individual brain size. We assessed obesity-related gray matter volume differences on a whole-brain level. According to our specific hypothesis of an association between NAcc volume and willingness to exert effort (fraction of yes decisions), as well as between NAcc volume and measures of food craving (wanting ratings and task induced implicit food craving), we utilized a ROI-based approach with a NAcc mask obtained from the Harvard-Oxford Subcortical Structural Atlas within FSL 4.1 to test for related effects. Family-wise Error (FWE) correction for multiple comparisons was applied at the cluster level with a statistical threshold of $p < 0.05$.

RESULTS

Demographics, Ratings, and Questionnaires

Statistical assessment of demographic, rating, and questionnaire data as well as subjects' maximum hand grip forces, mean reaction times and fraction of decisions to exert effort over the whole task are summarized in **Table 1**. Subject groups did not differ with respect to age and educational background, depressive symptoms, reward or punishment sensitivity, and chronic stress levels. Self-reported body dissatisfaction differed significantly between groups [$F_{(3,\ 56)} = 22.62$, $p < 0.001$]. *Post-hoc T*-Test revealed that lean men reported lower body dissatisfaction than obese men [$T_{(26)} = -7.16$, $p < 0.001$] and lean women reported lower body dissatisfaction than obese women [$T_{(27)} = -4.10$, $p < 0.001$]. Further, lean men reported lower body dissatisfaction than lean women [$T_{(26)} = -4.46$, $p < 0.001$].

Participants did not significantly differ with respect to hunger prior to task or task-induced implicit food craving (see **Table 1**). While we found no differences with respect to self-reported liking of the fruit items that entered the task, subjects differed with respect to liking of the sweet snack items [$H_{(3)} = 8.13$, $p < 0.05$]. *Post-hoc* analysis revealed that lean women showed higher liking of sweet snack items than obese men [$H_{(2)} = 16.6$, $p < 0.01$]. All other pairwise comparisons did not survive correction for multiple comparisons. Importantly, all four subject groups showed comparable wanting ratings of the individual sweet snack and fruit items that entered the task (see **Table 1**).

Maximum hand grip force assessed prior to the task differed between subject groups [$F_{(3,\ 56)} = 34.96$, $p < 0.001$, **Table 1**]. *Post-hoc T*-Tests revealed that this was related to gender differences. Both lean and obese men showed higher hand grip force compared with lean women [obese men: $T_{(28)} = 7.59$, $p < 0.001$; lean men: $T_{(26)} = 6.80$, $p < 0.001$] and obese women [obese men: $T_{(27)} = 7.35$, $p < 0.001$; lean men: $T_{(25)} = 6.56$, $p < 0.001$]. In the subsequent task, effort levels were adjusted to individual maximum hand grip force.

Reaction Time and Cost-Benefit Decisions

Task-Design

Subjects carefully evaluated the tradeoff between costs and benefits. This was reflected in subjects' reaction times by a three-way interaction of effort magnitude, reward magnitude, and fraction of decisions to exert effort ($X^2 = 42.46$, $p < 0.001$, **Figure 1E**). Subjects decided fastest to grip in trials involving low effort (le) and high reward (hr) levels and were slowest in accepting cost-benefit offers in trials with high effort (he) and low reward (lr) magnitude [EMM(le/hr) = 578.61ms, EMM(he/lr) = 621.68ms, $p < 0.001$]. For deciding to reject cost-benefit offers the opposite pattern was observable [EMM(le/hr) = 737.18 ms, EMM(he/lr) = 626.26 ms, $p < 0.001$]. This was mirrored in subjects' decisions, i.e., they more often chose to grip in low compared with high effort trials ($X^2 = 200.74$, $b = 1.56$, $p < 0.001$, **Figure 1C**) and in high compared with low reward trials ($X^2 = 160.44$, $b = 2.33$, $p < 0.001$, **Figure 1C**). As expected, individual wanting ratings of included reward items correlated positively with the amount of exerted effort ($X^2 = 17.15$, $b = 0.29$, $p < 0.001$) and subjects' willingness to invest effort to receive rewards decreased over time ($X^2 = 67.17$, $p < 0.001$, **Figure 1B**). Comparing reward categories, we observed that subjects significantly faster decided in trials that yielded money than fruit items ($X^2 = 5.68$, $b = -17.6$, $p < 0.05$). Subjects also more often chose to grip for money than for sweet snacks ($X^2 = 16.47$, $b = 1.14$, $p < 0.001$, **Figure 1D**) or fruit pieces ($X^2 = 5.1$, $b = 0.72$, $p < 0.05$, **Figure 1D**).

Whether reward or effort demand was depicted first also influenced subjects' task performance. They decided faster whether to grip or not in trials in which reward stimuli were displayed before effort demands were shown ($X^2 = 41.69$, $b = -29.63$, $p < 0.001$). In these trials, subjects were also more likely to invest effort than in trials, in which effort levels were shown first ($X^2 = 6.97$, $b = 0.1$, $p < 0.01$). Taken together, these results support the ecological validity of our approach.

Obesity- and Gender-Related Effects

Throughout the task, lean subjects responded faster than obese participants ($X^2 = 4.67$, $b = -44.05$, $p < 0.05$, **Table 1**). We found no association of obesity and general amount of exerted effort throughout the task (**Table 1**). However, we observed a significant obesity by gender interaction ($X^2 = 5.12$, $p < 0.05$): Obese men less likely invested effort than lean men [EMM(lm) = 0.81, EMM(om) = 0.63, $p < 0.01$, **Table 1**]. This obesity-related difference was not observable in women [EMM(lw) = 0.71, EMM(ow) = 0.75, $p = 0.59$].

As hypothesized, our data showed an obesity by reward category interaction ($X^2 = 7.92$, $p < 0.05$, **Figure 2**): Obese compared with lean subjects were less likely to grip on trials yielding sweet snacks [EMM(l) = 0.71, EMM(o) = 0.5, $p < 0.05$] but not on trials involving fruit pieces or money as a reward. Obese subjects more often decided to grip for money and for fruits than for sweet snacks [EMM(mo) = 0.85, EMM(sw) = 0.5, $p < 0.001$; EMM(fr) = 0.66, $p < 0.01$]. Lean subjects equally often decided to grip regarding the three reward categories.

Reaction time analysis further revealed a significant interaction of gender by reward category ($X^2 = 9.05$, $p < 0.05$, **Figure 1F**). Men decided faster in trials that yielded monetary reward (mo) compared to fruit (fr) and sweet snack (sw) trials [EMM(mo) = 590.21 ms, EMM(fr) = 631.38, $p < 0.01$; EMM(sw) = 625.79, $p < 0.01$], but no such differentiation was found in women. With respect to subjects' decisions, we found a significant effort level by gender interaction [$X^2 = 5.32$, $p < 0.05$]. Specifically, women were more sensitive to an increase in effort demands than men, i.e., women were more likely to invest effort in low effort trials than men, but men more often decided to exert effort in high effort trials than women [low effort: EMM(w) = 0.88, EMM(m) = 0.85; high effort: EMM(w) = 0.51, EMM(m) = 0.56; $X^2 = 186.86$, $p < 0.001$]. We did not find significant interactions of trial block by obesity, trial block by gender or obesity by gender and reward category.

Influence of Age, Chronic Stress, Reward/Punishment Sensitivity, and Body Dissatisfaction

Across all subjects, reaction times marginally increased ($X^2 = 3.53$, $b = 3.02$, $p < 0.06$) and subjects' amount of expended effort decreased with increasing chronic stress ($X^2 = 5.47$, $b = -0.03$, $p < 0.05$, **Figure 3A**). Further, subjects' punishment sensitivity correlated negatively ($X^2 = 11.34$, $b = -0.14$, $p < 0.001$, **Figure 3B**) with the fraction of decisions to invest effort. Age and reward sensitivity had no significant impact on subjects' decisions, though with increasing age reaction times increased ($X^2 = 6.03$, $b = 7.57$, $p < 0.05$).

Following our hypothesis, we finally investigated if body dissatisfaction had an impact on cost-benefit decisions. We assessed a four-way interaction of reward category, obesity, gender, and reported body dissatisfaction. This interaction was significant ($X^2 = 37.33$, $p < 0.001$, **Figures 4A–D**). However, contrary to our hypothesis, parameter estimates of the model showed that body dissatisfaction negatively correlated with the likelihood to grip for sweet snacks in obese men ($X^2 = 5.48$, $b = -0.05$, $p < 0.05$, **Figure 4A**), but not in obese women ($X^2 = 1.44$, $b = 0.05$, $p = 0.23$, **Figure 4B**).

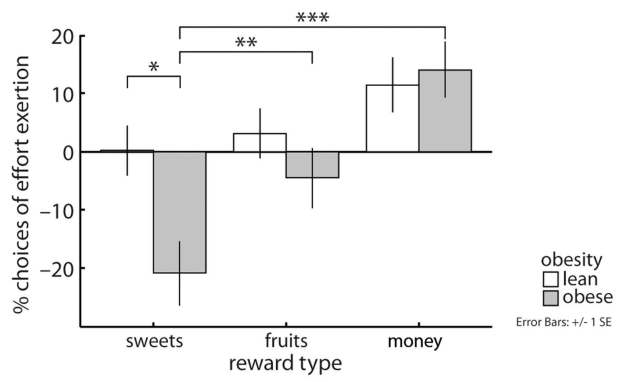

FIGURE 2 | An interaction between reward category and obesity revealed that obese compared with lean subjects less often chose to grip for sweet high-caloric snacks, but performed similarly with respect to fruits and money as rewards. Obese subjects also more often decided to grip for money and for fruits than for sweets, this effect was not apparent in lean subjects. Depicted values are corrected for factors and covariates within the respective GEE model. Asterisks indicate significance within the respective GEE model reported in the Results Section.

Structural MRI

On a whole-brain level, obese compared with lean subjects had lower gray matter volume in bilateral clusters of ventrolateral PFC, comprising inferior frontal gyrus (**Table 2**, **Figure 5A**). We found no positive association of obesity and gray matter volume.

ROI analysis of NAcc gray matter volume yielded a significant positive correlation of implicit food craving and bilateral NAcc volume (**Table 2**, **Figures 5B,C**). We found no significant association of NAcc volume and subjects' willingness to exert effort, or explicit wanting ratings.

DISCUSSION

Here we show that the trade-off between costs in terms of physical effort and food reward in obese subjects may be more complex than expected up to date (Epstein et al., 2007; Giesen et al., 2010). Our data demonstrate for the first time that obese compared with lean subjects may be less willing to invest physical effort for high-caloric food reward in particular. Importantly, in a recent study that utilized button presses to obtain a reward, we observed that obese men were less sensitive to changes in motivational value of snack food, as induced via a devaluation procedure, than lean men (Horstmann et al., 2015a). This indicates that the obesity-related difference observed here is specific for physical effort, emphasizing the importance of taking into account physical effort as a potential target for therapeutic interventions and changing every day food choices of obese subjects possibly via increasing effort barriers, e.g., by rearrangement of food assortments in cafeterias and supermarkets. Two recent studies in humans (Epstein et al., 2007; Giesen et al., 2010) revealed contradictory results to our finding, which most likely reflects methodological differences. We used three distinct reward categories and, in contrast to previous studies that employed button presses, assessed physical effort via a handgrip dynamometer which has proven to be a reliable tool to capture physical exertion (e.g., Treadway et al., 2009; Wardle et al., 2012). Notably, findings in rodents related to cost-benefit decision-making alterations in obesity models are also diverse. While some studies show an increased motivation to work for high-caloric sweet food in rodent models of obesity (la Fleur et al., 2007; Hajnal et al., 2008; Narayanaswami et al., 2013), there is also growing evidence for a decreased willingness to exert effort for food high in fat and

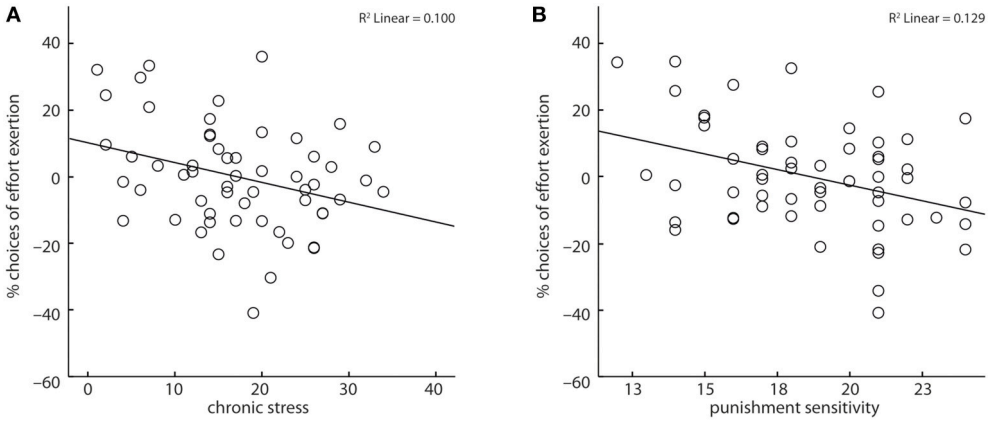

FIGURE 3 | Chronic stress **(A)** and punishment sensitivity **(B)** correlated negatively with the likelihood of choosing to exert effort. Depicted values are corrected for factors and covariates within the respective GEE model.

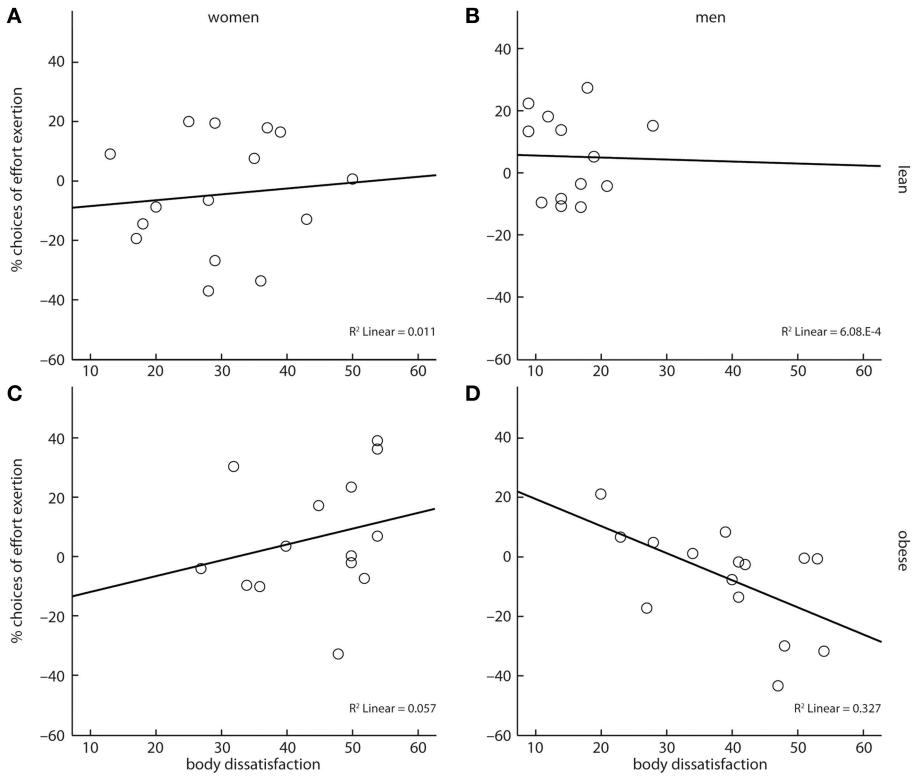

FIGURE 4 | A four-way interaction between reward category, obesity, gender, and body dissatisfaction showed that obese men's cost-benefit decisions regarding sweet snacks were negatively correlated with their self-reported body dissatisfaction **(D)**. No such association was observed for lean women **(A)**, lean men **(B)**, and obese women **(C)**. Depicted values are corrected for factors and covariates within the respective GEE model. Asterisks depict significance within the GEE model.

sugar (Davis et al., 2008; Shin et al., 2011; Harb and Almeida, 2014). This reduced motivation to work for food reward may partly be associated with an attenuated dopamine metabolism, possibly reflecting adaptive processes such as heightened DA level within NAcc as a result from a prolonged energy-dense diet (Davis et al., 2008). Studies in humans show reduced striatal D2/D3 receptor availability in obese compared with lean subjects that may relate to heightened tonic DA as well (Horstmann et al., 2015b). Following this, our findings may hint at similar associations between disturbances in dopaminergic function and reduced motivation to exert effort for high-caloric food in obese individuals.

The observed obesity-associated difference in cost-benefit evaluation was modulated by self-reported body dissatisfaction and gender. In obese men, but not in obese women, the likelihood of choosing to invest physical effort for high-caloric sweet snacks was negatively correlated with body image discontent. We expected to observe an impact of body dissatisfaction on cost-benefit decisions rather in obese women than in obese men, due to the supposed greater burden of stigmatization in obese women (Gray et al., 2011; Forrester-Knauss and Zemp Stutz, 2012; Forste and Moore, 2012). Our opposing observation hints at a greater awareness and impact of weight discrimination on behavior in men than expected to date. In accordance, Lieberman et al. (2012) recently reported that men showed greater negative attitudes toward obesity than women. Further, they found that BMI positively correlated with the strength of negative attitudes toward obesity in men but not in women. The higher the BMI of their male participants was, the more they were concerned with the fear of getting obese. In addition, frequency of consuming fast-food is higher in men than in women and correlates positively with BMI (Dave et al., 2009; Anderson et al., 2011). A prolonged period of consuming convenience products may foster the association between palatable food and low effort demands. Further, prolonged consumption of palatable food can lead to a decrease in liking of these food items (Clark et al., 2010).

The modulating effect of gender on the observed obesity-associated differences in cost-benefit evaluation may also be related to differences in dopaminergic tone within the fronto-striatal pathway (e.g., Haaxma et al., 2007). Estrogen level was shown to impact measures of dopamine-related cognitive performance and inhibitory control (Colzato et al., 2010; Jacobs and D'Esposito, 2011; Silverman et al., 2011; Hampson and Morley, 2013). In rodents, modification of estradiol levels was previously related to alterations in cost-benefit decision-making (Uban et al., 2012).

Subjects choose to invest effort to receive a certain reward if their subjective motivational value of the reward item exceeds the respective effort costs. Accordingly, individual wanting ratings correlated positively with subjects' choices. Notably, we also tested whether controlling for liking of the food items would change our obesity-associated results. This was not the case. Thus, behavior in our task was driven by the current motivational value of the rewards. Literature on obesity-associated differences with respect to wanting and liking of sweet snack food is still inconsistent. Despite studies showing a positive relationship between the reinforcing value of snack food and body weight (Ouwehand and de Ridder, 2008; Goldfield et al., 2011; Ochner et al., 2012), there is also evidence of a possible negative association (Cox et al., 1998; Gearhardt et al., 2014). Consumption of high-caloric food over a prolonged period can decrease liking of energy-dense food (Clark et al., 2010; Vucetic et al., 2011).

Women were more sensitive to increases in physical effort demands than men. This is in accordance with previous findings, indicating that men rated perceived exertion lower than women (Skatrud-Mickelson et al., 2011). A possible contribution to this gender-associated difference may arise from motivation intensity theory, indicating that men are more likely to be motivated by performance incentives (Barreto et al., 2012). Further, Perciavalle et al. (2010) showed that motor cortex in women is more sensitive to increases in circulating blood lactate levels than men's motor

TABLE 2 | Results from the VBM analysis in a subsample of 42 subjects.

	MNI-coordinates (peak voxel)	Number of voxels	Z-Score
LEAN > OBESE SUBJECTS (WHOLE-BRAIN)			
Right inferior frontal gyrus	54, 39, 9	1134	4.43
Left inferior frontal gyrus	–50, 30, 18	2091	4.73
IMPLICIT FOOD CRAVING (ROI-BASED)			
Right NAcc	10, 15, –11	158	3.64
Left NAcc	–3, 14, –2	30	3.63

Lean (23) compared with obese subjects had higher gray matter volume in bilateral inferior frontal gyrus. NAcc volume correlated positively with implicit food craving severity.

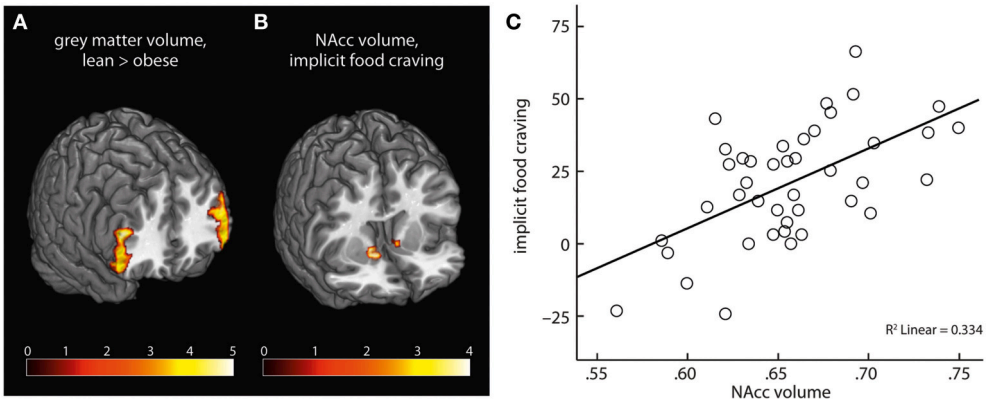

FIGURE 5 | Obese subjects had lower gray matter volume in bilateral PFC compared with lean participants **(A)**. NAcc volume positively correlated with severity of implicit food craving **(B,C)**.

cortex, hinting at sensitivity differences of physical exertion on a neural level.

Subjects' punishment sensitivity negatively correlated with their willingness to exert effort. This indicates that in our task design, effort exertion via pressing a handgrip device was perceived as physically demanding by the participants. This is an important aspect regarding the comparability with studies that used button presses as a measure of effort costs and that reported different results with respect to obesity (e.g., Giesen et al., 2010). Punishment sensitivity is associated with dopaminergic tone, specifically within the right frontal cortex and striatum (e.g., Maril et al., 2013). On a neural level, individual tonic dopamine level differences within the right fronto-striatal pathway may thus have contributed to sensitivity differences with respect to effort demands in our task.

Notably, self-reported chronic stress levels were negatively associated with subjects' likelihood of choosing to grip for rewards. This novel finding in humans is in accordance with a recent observation in rodents (Shafiei et al., 2012) that acute stress diminished the preference of rats to exert high effort levels to receive rewards. Stress is known to affect dopaminergic transmission within the fronto-striatal circuitry (Roth et al., 1988; Abercrombie et al., 1989; Davis et al., 1994; Latagliata et al., 2014). Since the same dopaminergic pathways are involved in processing effort-related information during cost-benefit decision-making (Walton et al., 2003; Schweimer and Hauber, 2006; Salamone et al., 2007; Salamone and Correa, 2012), stress may alter cost-benefit decision-making via modifying dopamine transmission in fronto-striatal dopaminergic target regions.

With respect to brain structure, we found lower gray matter volume in bilateral PFC comprising large parts of inferior frontal gyrus in obese compared with lean participants in a subsample of 42 participants. IFG is involved in inhibitory control mechanisms to guide behavior in a goal-directed manner among a variety of other processes (e.g., Aron et al., 2004; Swann et al., 2009). Hypo-functioning and lower gray matter volume within IFG have been related to obesity and disordered eating before (Batterink et al., 2010; Sweet et al., 2012; Balodis et al., 2013; Brooks et al., 2013). Regarding the motivation to overcome physical effort, Treadway et al. (2012) found that dopamine responsivity within IFG among other regions positively predicted willingness to exert effort in trials entailing high effort demands but low reward probabilities. In line, Massar et al. (2015) recently showed that IFG is critical for coding effortful demands. In contrast to our recent findings (Horstmann et al., 2011), we did not observe a positive association of obesity and gray matter volume in reward related areas or a modulatory effect of gender on gray matter volumetric differences regarding obesity. This may be related to the relatively small sample size compared with the former study.

As hypothesized, gray matter volume of NAcc positively correlated with an implicit measure of task-induced craving for food, as assessed by differences in subjects' hunger ratings before and after task execution. This is in line with recent findings that showed NAcc activity to correlate with craving severity in smokers (Kober et al., 2010). As we only assessed brain structure in this study, the next crucial step is to assess brain function during cost-benefit decision-making, to follow up on this finding. Associations between local gray matter volume and BOLD activation are complex, and dependent on the specific region of interest and the respective task among a multitude of other factors. Besides no direct associations (Guo et al., 2015) there are also studies showing a positive (Kalpouzos et al., 2012; Pujol et al., 2013) but also a negative correlation between local gray matter volume and BOLD response (Johnson et al., 2000; Bartrés-Faz et al., 2009; Kalpouzos et al., 2012).

Subjects' reaction times were modulated by reward and effort magnitude in a differential manner for yes and no decisions. Thus, subjects carefully evaluated reward and effort information and integrated both to form a decision. In line with this observation, Basten et al. (2010) recently proposed that cost-benefit decisions were established in an analogous way to perceptual decisions, i.e., the brain weighs costs and benefits by accumulating the difference signal of both on a neural level until a decision threshold is reached. Further, participants with obesity responded slower throughout the task than lean subjects. This is a common finding with respect to both simple (e.g., Khode et al., 2012; Gentier et al., 2013; Hagger-Johnson et al., 2014) and cognitive more demanding tasks (e.g., Nederkoorn et al., 2012; Gentier et al., 2013; Kamijo et al., 2014). In addition, men decided faster in trials involving monetary compared to food reward. This is congruent with recent observations that men but not women responded faster in a reaction time task involving monetary compared with social reward and that men revealed a differential BOLD activation pattern during anticipation of the distinct reward types (Spreckelmeyer et al., 2009).

In conclusion, our novel findings shed new light on obesity-related alterations in cost-benefit decision-making. Former findings that obese individuals may be willing to work harder for high-caloric food are challenged. Moreover, obese men seem to be more affected by concerns about body shape and possibly by related stigmatization than previously expected. This is an important issue for therapeutic strategies aiming at weight reduction and reducing stigmata in obese men. Further, increasing effort barriers for high-caloric food in food and eating environments (e.g., cafeterias, supermarkets), for example, by repositioning food assortments, may prove as a powerful tool to influence eating behavior. Additionally, therapeutic interventions aiming at altering psycho-social burdens such as stress may help to positively influence everyday-life effortful decisions and thereby reduce positive energy-balances in obese individuals.

AUTHOR CONTRIBUTIONS

DM, AH, BP, AV, and JN conceived and designed the experiment, DM acquired data, DM, AH, JN performed data analysis. DM, AH, BP, AV, and JN prepared and revised the manuscript. JN supervised the study.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

3 Summary

Zusammenfassung der Arbeit

Dissertation zur Erlangung des akademischen Grades Dr. rer. nat.

Obesity is associated with insufficient behavioral adaptation

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Obesity is one of the major health concerns nowadays according to the World Health Organisation (WHO global status report on noncommunicable diseases 2010, [189]). Thus, there is an urgent need for understanding obesity-associated alterations in food-related and general cognition and their underlying structural and functional correlates within the central nervous system (CNS). Neuroscientific research of the past decade has mainly focussed on obesity-related differences within homeostatic and hedonic processing of food stimuli. Therein, alterations during anticipation and consumption of food-reward stimuli in obese compared with lean subjects have been highlighted (e.g. [167, 166]). It seems that obese compared with lean individuals show heightened anticipatory but reduced consummatory brain responses to food reward sitmuli (e.g. [165, 32]). This indicates that obese subjects show a discrepancy between reward expectation and actual reward experience from food. Despite this difference between expectation and experience, obese individuals do not seem to downscale their food reward expectations and adapt their eating behavior accordingly.
Within the CNS, eating behavior is controlled by neural structures that are implicated in homeostatic and hedonic aspects of food intake (e.g. [15, 123, 124]). While homeostatic

control of food intake delineates the organism's maintenance of energy balance, hedonic food intake refers to eating due to the rewarding experience of eating in the absence of homeostatic needs. This is critically modulated by the mesolimbic and mesocortical dopaminergic (DAergic) pathways (e.g. [11, 181]). Furthermore, the CNS circuitries that control hedonic and homeostatic aspects of eating behavior intersect within the DAergic system [51, 125, 124].
Recently, evidence accumulates that obesity may be associated with more general disturbances in brain structure and function similar to those observed in addiction disorders [66, 95, 174]. In line with this, the DAergic pathways within the fronto-striatal system seem to play a key role in the observed obesity-associated differences [116, 192]. Obese individuals show alterations in the availability of D2-like receptors within striatum [185, 40]. We assume that this at least partly results from disturbances in tonic DA levels in obese compared with lean individuals [86]. Proper DAergic transmission is essential for the maintenance of flexible goal-directed behavior. Within striatum, DAergic signaling is believed to facilitate efficient behavioral adaptation by coding the difference between our expectations and actual outcomes of our actions, so called prediction errors (PEs) [151, 119]. An imbalance between tonic and phasic DA transmission may impede efficient coding and utilization of PEs for behavioral adjustment. Presumably this would attenuate the capability of behavioral adaptation in obese compared with lean individuals in a variety of tasks, not only in relation to food approach behavior but also outside of a food reward context. Besides its key role in learning-related behavioral adaptation, mesolimbic DA is also heavily implicated in motivational drive, that is overcoming effort costs to receive rewards [144, 145]. In particular, DAergic tone is known to modulate intrinsic motivational vigor [79]. If obese individuals are sensitive to changes in physical effort, an easily implementable strategy to change unhealthy eating habits in obese individuals may be to increase effort barriers in cafeterias and supermarkets for unhealthy high-caloric snack food.

This thesis contains five experimental studies. In studies 1-4, we investigated several pivotal facets of behavioral adaptation in obese compared with lean participants within and outside of the food context and its association with dopamine transmission. In study 5, we assessed if physical effort differentially affects cost-benefit decision-making regarding food and non-food rewards in obese compared with lean individuals. Besides assessment of behavioral alterations, we were interested in associated differences within brain structure and brain function. This was accomplished by voxel-based morphometry (VBM) and functional magnetic resonance imaging (fMRI). To assess PE-related adaptation of behavior, we utilized computational modeling. With the help of positron emission tomography (PET) and Parkinson's disease (PD) and Huntington's disease (HD) patients, we validated our computational model and tested specific hypothesis regarding the associa-

tions between alterations in DA transmission and specific deficits in PE-related behavioral adaptation. We also assessed gender as a modulating factor in three of the five studies, as gender is believed to modulate DAergic transmission [84, 78, 197], and has been shown to impact on the neural control of food intake [186] and local grey matter volume [107].

In more detail, the first study tested behavioral adaptation in a food reward context. Here, we aimed at revealing attenuated adaptation of food approach behavior in obese men following changes in motivational value of related snack food items. Therefore, we utilized a devaluation task, adapted from animal research [29]. We found that BMI negatively correlated with the impact of changes in motivational value of snack food items on food approach behavior. Thus, obese men showed a reduced behavioral adaptation to changes of incentive motivation within a snack food environment. This likely translates into a more habit-like control of behavior similar to compulsion as revealed in drug addiction. On the behavioral level, a long history of excess eating may lead to strong stimulus-response, that is food cues and food intake, associations, resulting in the development of a more automated, habitual food intake. Interestingly, individuals with obesity and drug addiction show similar alterations in blood-oxygen-level-dependent (BOLD) activation in fronto-striatal regions during reward processing [66]. A common neuronal basis may be disturbances in DAergic transmission within meso- and cortico-limbic loops. Attenuated tonic DA levels may explain findings of heightened DA receptor availability within striatum in moderately obese individuals [86] and may at least partly translate into the here observed attenuated adaptation of food approach behavior.

In the second study, we investigated obesity-associated alterations in behavioral adaptation in a more abstract gambling task (a modified version of the 'Iowa Gambling Task', [7]) outside of a food environment. In the task participants are free to draw cards from two card decks. Each card either results in positive or negative points. One card deck is advantageous as it results in a long-term positive outcome, whereas choosing from the other decks leads to a long-term loss. Participants have to learn to trade-off short-term rewards against long-term losses and adequately adapt their choice behavior to maximize their long-term outcome. In addition, we assessed local gray matter volume differences with the help of VBM in a separate large cohort of lean and obese individuals. For both behavioral and grey matter volume assessments, we were interested in gender-specific findings. We revealed grey matter differences within both the brain's hedonic and homeostatic control system of food intake in obese compared with lean individuals. Increased gray matter volumes within medial orbitofrontal cortex (mOFC), Nucleus accumbens (NAc) and hypothalamus may translate into altered saliency processing of food reward stimuli and related excess food intake. In female obese subjects, this was accompanied by increased gray matter volumes within dorsal striatum together with reduced gray matter volumes in dorsolateral prefrontal cortex (dlPFC). Both structures play opposing roles

in the balance of habitual and goal-directed control of behavior. These findings foster our assumptions on a neuronal level of attenuated goal-directed adaptation of behavior in favour of a more habit-like action control in obese individuals. This was mirrored in an attenuated adapation of gambling behavior to achieve a long-term positive outcome in obese compared with lean women. A reduced sensitivity to and/or an attenuated utilization of negative feedback may at least partly explain the observed maladaptive behavior in obese women. In addition to the related alterations in local grey matter volume, we assume that this may be associated with reduced tonic DA transmission within striatum [86].

In the third study, we were interested in associations of dopamine transmission and behavioral adaptation to reveal possible underlying mechanisms of related alterations observed in obesity. For this purpose, we built a computational reinforcement learning model that is capable of linking the intrinsic utilization of a DAergic teaching signal, that is PEs, with subjects' capability of behavioral adaptation during learning. We used a complex implicit stimulus-response learning task (Weather Prediction Task (WPT), [98]) in which subjects had to learn to associate complex stimulus-patterns with a binary outcome. To directly relate PE-related adaptation of response behavior with striatal DAergic transmission, we tested healthy participants task-performance inside a PET scanner. Availability of striatal D2 receptors was assessed by computing binding potential (BP_{ND}) of the radiotracer Raclopride ([^{11}C]RAC). We further tested PD patients on versus off levodopa medication, to test if alterations in tonic DA levels within ventral striatum are associated with reduced learning from negative PEs in particular. To assess if disturbances within the direct pathway of the basal ganglia relate to changes in learning from positive PEs, we also compared early HD patients' with healthy subjects' task performance. We found that strength of learning from positive PEs was linearly related with phasic DA release in ventral striatum during learning. Strength of utilizing negative PEs for behavioral adaptation was associated with tonic DA levels in ventral striatum in an inverted u-shaped fashion. As expected, PD patients on levodopa were specifically impaired in learning from negative PEs, whereas early HD patients showed heightened utilization of positive PEs for subsequent behavioral adjustment.

Based on these findings we employed the same implicit learning task and the same computational model in study 4, to assess PE-related adaptation of behavior in obese compared with lean individuals. Subjects performed the task inside an MRI scanner to relate behavioral findings with fMRI-related BOLD activation. We were specifically interested in obesity associated differences in processing and utilization of PEs within the brain. To relate differences in PE-utilization with alterations in PE-modulated functional connectivity, we computed a psycho-physiological interaction (PPI) analysis. We hypothesized that obese compared with lean participants show reduced utilization of negative PEs in

particular for behavioral adaptation during learning, possibly due to an altered DAergic tone within striatum. We expected that this would be mirrored in reduced PE-related processing within the brain of obese subjects or that this would be related to a reduced functional coupling subsequent to negative PEs. As expected, we found that obese individuals showed a reduced utilization of negative PEs in particular to adjust their response behavior appropriately. Besides reduced task-related BOLD activation within the fronto-striatal circuitry, reduced negative PE utilization was associated with attenuated functional coupling between ventral striatum and supplementary motor area (SMA) subsequent to negative feedback in obese compared with lean participants. Learning from negative PEs is assumed to be related to synaptic plasticity within the so called indirect pathway of the basal ganglia [35, 111]. Therein, DA D2-like receptors are believed to be sensitive to small dips within the tonic DAergic signal that are associated with negative PEs. Too low (or too high) extracellular tonic DA may impede the detection of these small dips by D2 receptors and thus may relate to a reduced transfer of this teaching signal to higher cortical executive regions such as SMA. Notably, we did not directly assess DA transmission in this lean and obese subject sample. But we validated our computational reinforcement learning model utilized here in study 3 in healthy participants that underwent PET imaging, as well as in PD and early HD patients. We could show that utilization of negative PEs for behavioral adaptation during learning was nonlinearly related to tonic DA levels as assessed with [^{11}C]RAC BP_{ND} within ventral striatum. Thus, we are confident that the reduced utilization of negative PEs in obese participants is likely related to alterations in tonic DA levels within ventral striatum.

In the fifth study we assessed if physical effort differentially affects cost-benefit decision-making regarding food and non-food rewards in obese compared with lean individuals. In each trial of this cost-benefit paradigm, subjects were presented with a certain reward item (one or four pieces of snack food, fruits or money) and were free to exert effort in a given magnitude with a handgrip device to receive the reward. In addition to testing lean and obese subjects' willingness to exert effort for the different reward categories, we also assessed subjects' local gray matter volumes with the help of VBM. We expected altered willingness to exert effort in obese compared with lean subjects in particular for high-caloric snack food, possibly driven by a context sensitive DAergic reward system [10]. Further, we expected NAc volume to correlate with task-induced food craving. As hypothesized, participants' NAc gray matter volumes correlated with food craving severity. This also proved the validity of our task design. Obese in contrast to lean subjects showed attenuated willingness to exert effort for high-caloric sweet snack food in particular. This is contradictory to a recent study in humans [69], but in line with several findings in rodents (e.g. [38, 80]). This reduced motivation to work for food high in fat and sugar may be related to an attenuated DA metabolism within ventral striatum,

possibly reflecting altered tonic DA levels ([38, 86]). Following this, obese individuals may be even more sensitive to physical effort demands during food purchasing than lean individuals. Increasing effort barriers, e.g. via simply rearranging food-assortments in cafeterias and supermarkets, may provide a promissing tool for improving food-choices in vulnarable individuals.

Taken together, the first four studies of our experimental work point at attenuated behavioral adaptation in obese compared with lean individuals in a broad range of tasks both within and outside of a food context. We found evidence on the behavioral level as well as within obesity-associated differences in brain structure and function. The observed alterations wihtin the DAergic fronto-striatal system support a shift from goal-directed, flexible behavior to a more rigid habitual action-control. Disturbances in striatal DAergic regulation, such as presumably attenuated tonic DA levels in moderate obesity, likely play a key role in the reduction of utilizing negative feedback for appropriate adjustment of behavior. These findings are highly relevant for understanding the underlying neural mechanisms of obesity-associated alterations in food-related and general behavior.

The only efficient long-lasting weight reduction therapy up to date is bariatric surgery [158]. But this highly invasive approach bears serious health risks and thus should only be regarded as the ultima ratio intervention (e.g. [137]). The development of drugs that specifically act on tonic DA levels may be one possible strategy to target attenuated behavioral adaptation on a neural level in obese individuals. As indicated by the increased physical effort sensitivity regarding snack foods in obese compared with lean subjects, increasing effort barriers for high-caloric foods may change unhealthy food purchasement habits in vulnerable individuals. In the near future, direct assessment of DAergic transmission in obese compared with lean subjects during perfomance of behavioral adaptation probing tasks is an important next step. Further, cost-benefit evaluation should be assessed in an fMRI and/or PET setting to analyze functional correlates of the observed behavioral and grey matter differences in obese compared with lean participants. Most importantly, longitudinal studies should be carried out to foster our understanding of possible obesity predisposing differences in DAergic regulation and changes therein caused by excess food intake [126].

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Erklärung über den wissenschaftlichen Beitrag

Erstautorenschaften:

1. Publikation 3 – *'The role of dopamine in positive and negative prediction error utilization during incidental learning e Insights from Positron Emission Tomography, Parkinson's disease and Huntington's disease'*

   David Mathar hat folgenden Beitrag als Erstautor geleistet:

   - Entwicklung der Forschungsfrage und des Studiendesigns
   - Entwicklung und Implementierung des computationalen Modells
   - Analyse der Daten
   - Schreiben des Artikels

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2. Publikation 5 – *'Is it Worth the Effort? Novel Insights into Obesity-Associated Alterations in Cost-Benefit Decision-Making'*

David Mathar hat folgenden Beitrag als Erstautor geleistet:

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A Declaration of authenticity

Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

Datum Unterschrift

B Curriculum Vitae

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C List of puplications

Kube, J., **Mathar, D.**, Horstmann, A., Kotz, S.A., Villringer, A., Neumann, J. (2017) Altered monetary loss processing and reinforcement-based learning in individuals with obesity. Brain Imaging Behav. 2017 Dec 29. doi: 10.1007/s11682-017-9786-8. [Epub ahead of print]

Mathar, D., Neumann, J., Villringer, A., Horstmann, A. (2017) Failing to learn from negative prediction errors: Obesity is associated with alterations in a fundamental neural learning mechanism. Cortex. 95:222-237. doi: 10.1016/j.cortex.2017.08.022. [Epub ahead of print]

Mathar, D., Wilkinson, L., Holl, A., Neumann, J., Deserno, L., Villringer, A., Jahanshahi, M., Horstmann, A. (2016) The role of dopamine in positive and negative prediction error utilization during incidental learning - insights from Positron Emission Tomography, Parkinson's disease and Huntington's disease. Cortex 90:149-162. doi: 10.1016/j.cortex.2016.09.004

Mühlberg, C., **Mathar, D**., Villringer, A., Horstmann, A, Neumann, J. (2016) Stopping at the sight of food - How gender and obesity impact on response inhibition. Appetite 107:663-676. doi: 10.1016/j.appet.2016.08.121.

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Freeden, W., Fehlinger, T., Klug, M., **Mathar, D.**, Wolf, K., (2009). Classical globally

reflected gravity field determination in modern locally oriented multiscale framework. J Geod, 83:1171-1191.

D Conference contributions

Mathar, D., Wiehler, A., Chakroun, K., Goltz, D., Peters, J. (2017) A potential link between gambling addiction severity and central dopamine levels - Evidence from spontaneous eyeblink rates in pathological gamblers and controls. Poster Presentation at the 47th Annual Meeting of the Society for Neuroscience (SFN), Washington DC, USA.

Mathar, D., Neumann, J., Villringer, A., Horstmann, A. (2014) Failing to learn from negative prediction errors. Obesity is associated with alterations in a fundamental neural learning mechanism. Talk and poster presentation at the 30th Annual Meeting of the German Society for Obesity, Leipzig, Germany.

Mathar, D., Horstmann, A., Villringer, A., Neumann, J. (2013) Obesity and body dissatisfaction impact willingness to work for food in men. Poster presentation at the 29th Annual Meeting of the German Society for Obesity, Hannover, Germany.

Mathar, D., Horstmann, A., Villringer, A., Neumann, J. (2013) A novel cost-benefit decision-making task reveals obesity- and gender-related differences in the weighing of reward and physical effort. Poster presentation at the 11th Annual Meeting of the Society for NeuroEconomics, Lausanne, Switzerland.

Mathar, D., Neumann, J., B. Pleger, Villringer, A., Horstmann, A. (2013) The impact of obesity, gender and impulsivity on fronto-striatal system function. Poster presentation at the 19th Annual Meeting of the Organization for Human Brain Mapping (OHBM), Seattle, USA.

Mathar, D., Neumann, J., B. Pleger, Villringer, A., Horstmann, A. (2013) The impact of obesity, gender and impulsivity on probabilistic stimulus-response learning. Poster presentation at the 11th Leipzig Research Festival, Leipzig, Germany.

Mathar, D., Neumann, J., B. Pleger, Villringer, A., Horstmann, A. (2012) The impact of obesity and gender on probabilistic stimulus response learning. Poster presentation at the 28th Annual Meeting of the German Society for Obesity, Hannover, Germany.

Mathar, D., Neumann, J., B. Pleger, Villringer, A., Horstmann, A. (2012) Do obesity and gender bias implicit multi-cue learning performance? Poster presentation at the Tübingen Spring school 'Methods to study the brain in action', Tübingen, Germany.

Mathar, D., Neumann, J., B. Pleger, Villringer, A., Horstmann, A.(2011) The impact of obesity and gender on performance and strategy use in a probabilistic stimulus-response learning task. Poster Presentation at the 41st Annual Meeting of the Society for Neuroscience (SFN), Washington DC, USA.

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