Conclusions: In summary, the population dopamine neurons in the VTA showed a similar response to a food predictive cue and sucrose reward over time. The GLP-1 agonist semaglutide reduces appetite but increases VTA DA signaling during reward collection while PYY and amylin agonists did not. Thus, peripheral GLP-1 analogue semaglutide impacts the dopamine reward pathways specifically during a consummatory reward rather than cue expectation.

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THE ROLE OF DOPAMINE AND FOOD REWARD IN BULIMIA NERVOSA

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Background: Bulimia Nervosa (BN) is a severe eating disorder, characterized by recurrent episodes of binge eating and inappropriate compensatory behaviour. BN is associated with a high disease burden and only half of the patients recover within 6 years after disease onset, indicating the need for better understanding of BN pathophysiology and improvements in treatment options. Dopamine and the brain's reward system play a key role in food reward and the regulation food intake. However, neuroimaging studies on food reward in BN are scarce and inconclusive, and the role of dopamine has not been studied. This study investigates whether patients with BN show aberrant dopamine release to food reward stimuli.

Methods: In the currently ongoing study, female BN patients and healthy controls undergo PET-MR scanning with the dopaminergic radioligand [18F]fallypride. Participants view images of palatable food while receiving sips of milkshake (food reward), as well as viewing neutral control images while receiving sips of water. PET data were preprocessed and analyzed using MATLAB and SPM. The linear simplified reference region model was used to obtain an 'activation' parameter, representing additional dopamine release in the food reward condition compared to the control condition. Volume-of-interest (VOI) based analysis was performed on the proportion of voxels with significant dopamine release to food reward in each VOI, using Wilcoxin signed rank tests to assess whether the number of voxels with significant dopamine release is significantly higher than zero (FDR corrected for number of VOI). Lenient (corresponding to p=0.01 uncorrected) and strict (corresponding to p=0.05 Bonferroni corrected for number of voxels in mask) voxel-based threshold were applied. The mask contained 30 VOI in the Striatum, Midbrain, Amygdala, Insula, Anterior Cingulate Cortex (ACC), and Orbitofrontal Cortex (OFC). Wilcoxon Two-Sample Tests were used to assess differences in dopamine release in BN patients and healthy controls.

Results: Healthy females (N=19, age 25±5, BMI 21.5±2.3) showed significant dopamine release to food reward in the amygdala, insula, ACC, OFC, and midbrain at a strict voxel-based threshold (pFDR≤0.001). The dorsal striatum only showed significant dopamine release at a lenient voxel-based threshold.

Preliminary results of BN patients (N=9, age 30±10, BMI 21.5±2.6) showed significant dopamine release to food reward in the insula, ACC, and OFC at a strict voxel-based threshold (pFDR<0.05). The caudate and midbrain only showed significant dopamine release at a lenient voxel-based threshold.

Compared to healthy controls, BN patients showed a trend towards less dopamine release to food reward in the amygdala and insula (pFDR<0.1, strict voxel-based threshold) and the midbrain as well as regions in the ACC and OFC (pFDR<0.1, lenient voxel-based threshold).

Conclusions: Rewarding food stimuli cause widespread dopamine release throughout the reward system. Despite the small sample size, we identified a trend towards less dopamine release to food reward in BN patients compared to healthy controls, which in line with several fMRI studies showing lower activity of the reward system to food stimuli in BN. Results from this ongoing study will improve our understanding of BN and might allow us to guide the optimization of behavioral treatment approaches.

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THE LINK BETWEEN PHYSICAL FITNESS AND THE REWARD SYSTEM IN SCHIZOPHRENIA

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Background: Obesity, weight gain and decreased physical fitness are severe complications of mental illness, especially schizophrenia, which constitute important predisposing factors for cardiovascular disorders. Thus, life expectancy of schizophrenic patients is lower than that of the general population. Schizophrenia is characterized by a dysregulated dopaminergic neurotransmission in the reward system, which currently poses the main target of antipsychotic medication [1]. The reward system is further linked to weight gain of otherwise healthy obese patients.

We hypothesize that alterations of the reward system lead to weight gain and lower physical fitness in patients compared to a group of healthy participants, indexed by less muscular strength, more body fat and lower VO2 max. With this study, we aim to establish a link between psychopathology and physical fitness to contribute to the development of alternative treatment options.

Methods: We will investigate 50 schizophrenic patients and 50 healthy volunteers, matched by gender and age. We have established a neuroimaging battery of two standardized fMRI tasks and a resting state measurement. We use a monetary incentive delay task to probe reward anticipation in the salience network as well as a delay-discounting-paradigm to test orbitofrontal evaluation strategies. Further, we make use of a battery of anthropometric measures providing information about body fat, muscular strength and maximal oxygen capacity in order to characterize the physical fitness status of the participants.

Psychopathology is assessed by the Positive and Negative Syndrome Scale, the Calgary Depression Scale for Schizophrenia as well as by self-rating scales, such as the Chapman Scale of Physical and Social Anhedonia and the WHO Disability Assessment Schedule. Moreover, we record diet, eating behavior and physical activity by using standardized questionnaires.

Results: Up to now, we have measured 24 patients (age = 37 ±12,8) as well as 18 gender and age- matched healthy volunteers (age = 34 ± 12,8). First tendencies reveal lower physical fitness and significantly higher body fat in the patient- (VO2 max = 27,9 ± 16,6; total body fat = 30,7 ± 7) compared to the healthy subject group (VO2max = 39,8 ± 10, p-value = 0.012; total body fat = 25,5 ± 8,3, p-value = 0.036). Physical fitness further negatively correlates with psychopathology (p-value ≤ 0.01). MRI data indicates a negative correlation between the cumulative lifetime dose of antipsychotics and activation of reward nuclei during reward anticipation in patients. Resting state data shows group differences as to functional connectivity of the reward system.

Conclusion: Follow-up analyses in up to 50 patients and 50 healthy controls will make use of the physical fitness data to split control and patient groups in a high- versus a low-fitness group. By studying reward dysregulation in patients and controls as well as low- versus high-fitness participants, we will not only understand disorder specific effects but the psychopathological as well as neural state of patients resilient to decline of physical fitness. Regarding future studies, this might contribute to a better understanding of how these important neural hubs of the reward system can be altered by fitness and lifestyle therapies.

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GUT MICROBIOTA MODULATE HYPOTHALAMIC AND HIPPOCAMPAL GENE EXPRESSION REGULATING EATING BEHAVIOUR, FOOD REWARD AND STRESS

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Background: The microbiota-gut-brain axis has been extensively studied for its impact on metabolic diseases, food intake behaviour, as well as stress-related disorders [1,2,3,5]. Homeostatic regulation of food intake is regulated mainly by the hypothalamus, while the hippocampus is important in the cognitive control of eating behaviour [1,4]. Moreover, changes in both brain regions have been implicated in chronic effects of stress [1]. The gut microbiota has been demonstrated to influence body fat regulating genes, especially leptin expression, in the hypothalamus and the brainstem [3,5]. However, it has never been demonstrated whether the gut microbiota modulates the hypothalamic and hippocampal expression of genes related to appetite, food reward and food intake behaviour. Our recent results suggest novel findings showing a modulation by certain gut microbiota strains of the hypothalamic and hippocampal gene expression regulating eating behaviour and stress *in vitro* and *in vivo*. In conclusion, we show the promising potential of certain human gut microbiota strains, especially the hit *B.Longum* PSY001, to be developed as a supplement in modulating stress, appetite, food intake behaviour and reward, and consequently, as part of possible treatment for metabolic and mental diseases.
Objective: The objective of this study is to investigate the effects of *B.Longum* PSY001 and other bacterial strains on hypothalamic and hippocampal expression of genes previously linked with the regulation of food intake and reward, satiety, glucocorticoid metabolism, and stress.
Methods: We analysed changes in gene (*Oxt, Ghrl, Ghsr, Drd2, Oprm1, Npy, Pomc, Agrp, Cart* and *Bdnf*), expression in adult (mHypoA2-28) and embryonic (mHypoE N41) hypothalamic and hippocampal immortalized murine cells following 2h exposure to *B.Longum* PSY001 as well as other bacterial strains. Next, we analysed hypothalamic and hippocampal gene expression following chronic administration of the *B.Longum* PSY001 in drinking water to Balbc and C57Bl6 mice.
Results: We demonstrated that supplementation with certain bacterial strains, including the *B.Longum* PSY001, was able to modulate expression of several orexigenic (including *Ghrl, Npy,* and *Agrp*) and anorexigenic (such as *Oxt* and *Pomc*) genes in hypothalamic and hippocampal cells. *B.Longum* induced an increased expression of *Oxt* and *Oxtr* (anorexigenic) and Pomc (orexigenic) genes in hippocampus of C57Bl6, in *Oxt* and *Cart* (anorexigenic) in the hippocampus of Balbc mice and the orexigenic Pomc gene in hypothalamus of Balbc mice. Additionally, *B.Longum* PSY001 increased *Bdnf, Nr3c1* and *Nr3c2* expression in hippocampus of C57Bl6 as well as hippocampal *Nr3c1* and *Bdnf* in Balbc.
Conclusions: We show the potential of certain bacterial strains to modulate the expression of genes involved in appetite, food reward, food intake behaviour and host metabolism in addition to stress *in vitro* and *in vivo*. Thus, highlights the promising therapeutic potential of these human gut microbiota strains to improve metabolic and mental health.
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IS DECISION-MAKING IMPAIRMENT AN ENDOPHENOTYPE OF ANOREXIA NERVOSA?

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Background: Patients with anorexia nervosa (AN) show altered decision-making ability [1]. Decision-making impairments are a recognized hallmark of patients with AN, putatively underpinned by dysregulations of the reward system. Most behavioural symptoms of AN could be read as consequences of impaired decision-making.
It is today unclear whether decision-making impairment is a trait marker, i.e. a stable endophenotype of AN [2], or a state parameter, i.e. being explained by present symptoms and associated comorbidity.
The aim of this study was to determine the endophenotypic nature of decision-making alteration and of its cognitive components in patients with AN.
Methods: Ninety-one patients with acute AN (A-AN), 90 unaffected relatives (UR), 23 patients remitted from AN (R-AN) and 204 healthy controls (HC) underwent the Iowa Gambling Task (IGT) and psychometric assessments.The IGT is a widely used test to assess decision-making alterations, simulating real life decision making by factoring reward and punishment [3]. Players have to choose between cards providing immediate rewards, with the risk of important losses, and cards associated to moderate gains, but also moderate losses. This task enables to profile impulsive behaviour, characterized by the preference of immediate gains despite negative consequences, to measure the capacity to learn from past experience, and the tendency for risk taking.The Prospective Valence Learning model (PVL) was employed to distinguish the cognitive dimensions underlying the decision-making process [4]. This mathematical approach, informed by cognitive neuroscience and Bayesian theories, allows a more precise analysis of the multiple processes involved in a cognitive task, and their quantitative comparison across specific populations. The PVL model is a performant and widely used model to explain the mechanisms underlying decision-making, already employed in studies on patients with AN. Performance at the IGT was compared between the four groups and then analyzed according to clinical and psychometric variables such as body mass index (BMI) and the score at the eating disorder inventory-2 (EDI-2).
Results: Patients with A-AN had worse performances at the IGT than UR, HC ($F(3,407) = 4.06$, $p<.01$) and R-AN even though the latter failed to reach significance. When analyzing decisional styles by the PVL models, it appeared that acute patients with AN had significantly higher aversion to losses than remitted patients, and their sensitivity to feedback was lower than HC and UR, but higher than R-AN ($p<.01$). In the group of patients with AN (A-AN + R-AN), the parameter of loss aversion was positively correlated with severity of psychopathology (EDI-2 score) ($r=.25$, $p=.01$), while sensitivity to feedback was correlated with BMI ($r=-.37$, $p<.01$) and the EDI-2 score ($r=.35$, $p=.01$).
Conclusions: Impaired decision-making represents a state-associated, cognitive hallmark of AN, since it is absent in unaffected relatives, healthy controls and patients remitted from AN. The aggravation of reward modulation along with illness progression may explain the persistence of symptoms despite their consequences on health [5]. This state-specific result of the decision-making process