GENERAL OBJECTIVE 1: To test whether eating behaviour and addiction share common susceptibility factors.

We analysed a large representative community sample of more than 3000 adolescents and young adults - data collected over more than 10 years. This provided extensive data on the incidence and co-occurrence of alcohol dependence, nicotine dependence and eating disorders, and provided evidence for three core factors (Key findings 1A-1C):

.... KEY FINDING 1A: The relationship between eating and addiction problems differs by age and gender.

By the end of the time span examined in our study (maximum age of 34), the rate of participants that had ever suffered from a substance use disorder (46%) was much higher than the rate of participants that had ever fulfilled criteria for a clinical or subclinical eating disorder (5%); 18% of the participants regularly consumed alcohol at baseline, and 33% were regular smokers. Strikingly, 89% of participants with any threshold or subthreshold eating disorder up to our last assessment were women, and only 11% were men. Concerning substance use disorders, 59% of cases were men, whereas 41% were women. Accordingly, there were significant gender differences for the distribution of both eating disorders and substance use disorder. For core eating-disorder symptoms, we found that single symptoms of anorexia nervosa and bulimia nervosa, e.g. underweight (27%) and undue influence of weight and shape on self-esteem (18%), were much more frequent than eating disorders. Again, eating-disorder symptoms were more common in females than in males.

... KEY FINDING 1B: Different eating disorders have different patterns of association with substance abuse disorders.

In the 12 months before the first assessment, there were no substantial associations between substance use disorders and anorexia nervosa, but bulimia nervosa was significantly associated with alcohol dependence, nicotine dependence, cannabis abuse and illicit drug abuse. However, over the lifespan of the participants, both anorexia nervosa and bulimia nervosa were significantly associated with substance use disorders. Bingeing and purging phenotypes of anorexia nervosa and bulimia nervosa were significantly associated with substance use disorders or with anxiety- and depressive disorders. On the other hand, restrictive or non-purging subtypes were not associated with substance use disorders (but were associated with depression).

… KEY FINDING 1C: Evidence for pathways involved in the relationship between eating and substance disorder onset.

In the risk factor analysis for eating disorders and substance use disorders, “gender” was the only risk factor predictive of all three outcome categories that were applied (ED, SUD, comorbid ED+SUD): Female gender increased the risk for eating disorders, but decreased the risk for substance use disorders, in accordance with previous studies. We found several risk factors predictive of at least two of the three

outcome categories: “Dysfunctional coping”, “novelty seeking” and “having not grown up with both biological parents” increased the risk for substance use disorders and comorbid ED+SUD. One novel finding was that having suffered from a “specific phobia in the last 12 months before baseline” predicted both eating disorders and substance use disorders. The risk for eating disorders was increased by: a somatoform disorder (i.e. a mental illness in which body symptoms cannot be linked to a physical cause), major depressive episode and hypomanic episode (i.e. a mood state characterized by persistent disinhibition and euphoric or irritable mood but generally less severe than full mania) in the last 12 months before baseline as well as a stressed financial situation at baseline. These factors could be early symptoms in the form of bodily sensations, affective vulnerabilities or acute life events, but could also be risk factors (or triggers for) a wider range of mental disorders. Suffering from “general anxiety disorder” in the last four weeks before baseline was a specific risk factor for substance use disorder. Interestingly, a “higher alcohol use at baseline” without fulfilling criteria for abuse or dependence was found to be predictive of a subsequent substance use disorder. A “stressed partnership at baseline” also lowered the risk for subsequent substance use disorder.

These findings may help to inform and improve future preventive interventions for both disorders. In a clinical (i.e. treatment-seeking) sample, both eating disorders and substance use disorders were much more prevalent than in the community-based sample. However, the co-occurrence of eating disorders and substance use disorders was much smaller in the clinical sample, showing the difficulty of comparing results from community studies with clinical studies at an epidemiological level.

GENERAL OBJECTIVE 2: To determine the relationship between psychopathology, stress, body weight and stimulatory behaviours of the reward system.

… KEY FINDING 2A: the view that `Food Addiction´ can cause obesity was not substantiated in adolescent psychiatric patients.

The NeuroFAST team has been heavily engaged in the “Food addiction” debate. In our consensus opinion article [1] we conclude that we lack an evidence base that individual foods/ingredients cause us to become addicted to them (which is very different to chemical substance addiction) and suggest that the term “eating addiction” better describes this behavioural disorder. We also point out that food addiction as defined with the Yale Food Addiction Scale only applies to a smaller subgroup of individuals with obesity (in addition to subjects who are <u>not</u> obese). By no means can obesity in the general population be explained by food addiction. For policy makers it is important to realize that prevention efforts in our opinion should preferentially target obesity per se. We view prevention efforts based only on the target food addiction as too narrow; in addition, the unsubstantiated underlying claim that nutrients/foods lead to a type of substance based addiction, will continuously be questioned (e.g. by the food industry), thus rendering the approach fraught to criticism entailing that stringent prevention efforts will most likely not be initiated. Instead, a focus on the obesogenic environment and ways and means to reduce the risk of susceptible individuals to develop obesity is required to allow the EU and the

respective countries to devise successful prevention strategies.

The problem inherent to the “diagnosis” of food addiction is best exemplified by our results pertaining to female patients with anorexia nervosa: These scored highest on the Yale Food Addiction Scale, indicating in addition to other data that `Food Addiction´ is associated with abnormal eating behaviour and cognitions that also characterize individuals with eating disorders. Accordingly, we perceive the need to develop an appropriate tool to disentangle the constructs of food and eating addiction from disordered eating behaviour and from classical eating disorders.

Overall, the diagnosis of “Food Addiction” applied to 16.5% of the 262 psychiatric inpatients (including those 32 inpatients with a diagnosis of an eating disorder). This rate is higher than that of 6% previously reported in a population based study sample. We found that Food Addiction and YFAS symptom counts were higher in the inpatient group than in the outpatient group. This could be due to the fact that the overall severity of psychopathology in inpatients is higher than in the outpatients. The prevalence of 7.5% in the outpatient group comes close to the reported prevalence rate in the general adult population. Whereas this finding requires independent confirmation, it would thus appear that mental illness is associated with above average rates of food addiction.

Presumably, this association is partially due to elevated rates of eating psychopathology in psychiatric patients, because we and others found a correlation between eating disorder symptoms as assessed with validated questionnaires and food addiction symptoms; these correlations remained significant even after exclusion of patients with eating disorders. The YFAS score was particularly correlated with eating disorder symptoms and behaviours associated with impulsivity and loss of control over eating.

Moreover, we find a positive correlation between Food Addiction symptoms and perceived stress. Perceived stress is known to increase the likelihood of eating disorders, behavioural addictions and both a negative and positive energy balance. Interestingly, patients with any substance use disorder (alcohol, nicotine, cannabis use disorder) had lower rates of food addiction than psychiatric patients without substance use disorders. If replicated, this would further indirectly cast doubt on a substance basis of food addiction, because subjects with a particular substance use disorder typically have elevated rates for additional use disorders.

Twelve months after initial assessment the former inpatients still had elevated levels of stimulatory behaviours, perceived stress, self-harm behaviour and eating disorder pathology. In particular and similar to baseline, 16.0% (13/81) fulfilled the criteria for a `diagnosis´ of food addiction according to the YFAS at the one year follow-up. However, the probability that the diagnosis was given at both time points was moderate only. Further studies are required to assess the medium and longer term stability of food addiction.

Apart from our research that focussed on food addiction we pursued other research questions. In the outpatients the magnitude of the effect of BMI-SDS on the score of the Childhood Behaviour Checklist (CBCL) was non-significantly lower than that of body fat percentage as determined by air displacement plethysmography. Nevertheless, measurement of body fat may be a more sensitive indicator for the relationship between body weight and mental symptoms, possibly also entailing the relevance of adipose tissue cytokines, hormones and peptides. We also found significant and moderate correlations with emotional eating, cognitions related to eating, weight and shape concern and BMI-SDS and with body fat percentage, respectively.

GENERAL OBJECTIVE 3: To study the common mechanisms of food reward and chemical drug reward, including to alcohol.

Just as the discovery of the fat-derived hormone, leptin, in 1994 provided a new window on brain function for energy balance, work in NeuroFAST explored the brain targets for another appetite-regulating hormone, ghrelin, a hormone secreted from the stomach. We showed that the brain pathways through which ghrelin operates interface not only food intake, but also food reward. These studies have paved the way for the identification of an endocrine gut-brain reward axis that drives motivated (craving-like) behaviour for food and psychostimulant drugs (including alcohol). Ghrelin is the only known appetite-regulating hormone to drive such behaviours and it does so by engaging brain pathways common to food and chemical drug reward. (Note that, the work reported here regarding ghrelin also addresses GENERAL OBJECTIVE 6 below).

… ***KEY FINDING 3A:*** Ghrelin, a metabolic signal, modulates the rewarding value of food**.**

We showed that ghrelin signalling in the brain is required for reward from chemical drugs such as alcohol [2, 3], cocaine and amphetamine [4, 5] and also for reward from food. Ghrelin orchestrates food-linked behaviours in rodents such as motivated behaviour for a sweet treat (lever-pressing paradigms)[6, 7] and food-anticipatory behaviour [8, 9], including anticipation of a sweet treat [10]. In these paradigms, the willingness to press a lever to get a sweet sugar pellet is increased by ghrelin and decreased by ghrelin antagonists, when delivered peripherally, centrally [7] or directly into the ventral tegmental area [6] (VTA, a key reward area that harbours the midbrain dopamine neurons and is involved in reward-driven motivation). The ability of sweet treats (chocolate) to condition a place preference (in which rats choose to spend more time in a chamber previously coupled with chocolate) was abolished by the ghrelin antagonist [11]. Furthermore, mice and rats show food anticipatory behaviour (heightened locomotor activity) just before scheduled periods of food access, and this was suppressed both in transgenic mice deficient in ghrelin receptors and in rats treated with a ghrelin antagonist [8, 10].

We made considerable progress in determining the neurobiological pathways underpinning ghrelin's effects, including hypothalamic midbrain and limbic targets[6, 11-19] as well as the downstream mechanisms involved uncovering the role of rapamycin (mTOR), which acts as a cellular sensor of changes in energy balance [19]. For example, we showed that it is possible to drive food-motivated behaviour by delivering ghrelin to the VTA but not to the nucleus accumbens (NAcc, another key reward area where the dopamine neurones terminate)[6]. With neurotransmitter/peptide antagonists we teased apart pathways that drive food intake versus those that drive food-motivated behaviour. For example, we provided evidence that the VTA to NAcc dopamine pathway is engaged by ghrelin for food-motivated behaviour but not for food intake [20]. This is important because it shows that reward behaviour can be regulated by appetite-regulating hormones. In cooperation with another EC-funded project, Full4Health, we showed that another gut-derived hormone, GLP-1 (glucagon-like peptide 1) also targets the reward circuits, in this

case, suppressing reward behaviour for food [21] and for alcohol [22]. The full impact of these findings have yet to be realised given that (i) ghrelin antagonists have not get been developed for human administration and (ii) drugs based on GLP-1 signalling are now in therapeutic use for the treatment of type 2 diabetes and even obesity.

…. KEY FINDING 3B: Reward consumption activates brain regions conventionally thought to be involved in homeostatic control of food intake.

Extensive neuroanatomical studies were undertaken to elucidate interactions between the endocrine hypothalamus and reward centres of the brain. For example, we mapped neuronal projections from the hypothalamus to the reward-initiating centre, the VTA. Anterograde and retrograde neuronal tract tracing techniques were used, combined with detection of specific neuronal markers, to identify the biochemical phenotypes of the neurons involved in this communication. We showed that, in addition to the well-established regulatory role of the lateral hypothalamus, the medially distributed hypothalamic nuclei are main regulators of the VTA [23], and many of the connections are reciprocal. Several nuclei in the hypothalamus connect with the VTA, including many that regulate energy balance (including the paraventricular nucleus and ventromedial nucleus). Surprisingly however, the arcuate nucleus contains relatively few neurons connecting with the VTA. This nucleus has been considered as the primary feeding center, as it receives information about the nutritional status of the body through hormones such as leptin and ghrelin. Within the hypothalamic nuclei, we found sub-populations of neurons projecting to dopamine neurons in the VTA, including corticotrophin releasing factor (CRF) neurons from the paraventricular nucleus, MCH and orexin neurons from the lateral hypothalamus projecting to dopamine neurons, and a few POMC neurons. The involvement of CRF neurons is particularly interesting as it indicates cross-talk with the hypothalamic pathways controlling stress responses (CRF neurons control the secretion of ACTH from the pituitary gland to control the adrenal gland). We also found connections between the mammillary nuclear complex and the VTA. Some of the nuclei within this complex are associated with the limbic system and relay hippocampal information via the thalamus toward the cingulate gyrus.

Both dopamine neurons and GABA neurons in the VTA were targeted by projections from hypothalamic nuclei. Interestingly, specific sub-populations of GABA neurons that are important inhibitory elements of the reward machinery were targeted. The projections from the hypothalamus to the VTA include both GABAergic and glutamatergic elements [23], so different hypothalamic nuclei can either facilitate and inhibit the VTA depending on whether the excitatory glutamate or the inhibitory GABA neurons are activated.

In humans, we found a connection between orexin neurons in the lateral hypothalamus and dopamine neurons in the VTA and substantia nigra [24]. Most of the orexinergic contacts targeted the dendrites of dopamine neurons, so this projection may play an important role in reward processing and drug abuse in humans, as well as in rodents. In addition, we found that the neurotransmitter acetylcholine was involved in the regulation of reward response by dopamine neurons in the human VTA.

… KEY FINDING 3C: Central kappa opioid receptors are a suitable drug target for the treatment of obesity and some associated co-morbidities.

Opioids are involved in a broadly distributed neural network that regulates eating behaviour, particularly consumption of highly palatable foods, and opioid antagonists attenuate both addictive drug taking and appetite for palatable food [25]. Opioids are important in reward processes leading to addictive behaviour such as self-administration of opioids and other drugs of abuse such as nicotine and alcohol. There are several opioid systems in the brain, and the one linked to abuse uses mu opioid receptors, at which morphine is a potent agonist. A different opioid system involves kappa opioid receptors, and the natural ligand for these receptors is dynorphin, which is densely expressed in several components of the appetite regulating networks of the brain, including in oxytocin neurons and in a subpopulation of neurons in the arcuate nucleus. While rats become dependent on morphine given chronically, they do not similarly become dependent on kappa agonists, so the involvement of this opioid system in appetite does not imply that food intake is addictive through this system in the way that morphine is addictive. However, the kappa opioid system is nevertheless an important system to understand in relation to food intake.

Importantly, we found that the kappa opioid receptor mediates some of the effects of ghrelin on energy homeostasis [26]. Specifically, we found that the orexigenic actions of ghrelin depend, at least in part, on the hypothalamic proDyn/KOR pathway This mechanism appears to be independent of ghrelin-induced hypothalamic AMPK activation but modulates levels of the transcription factors and orexigenic neuropeptides triggered by ghrelin. In addition, we showed that the KOR pathway is also involved in the central control of energy homeostasis exerted by other regulatory signals. Thus, we found that KOR are not only involved in the orexigenic effect exerted by MCH, but also in other central actions of this neuropeptide such as peripheral lipid homeostasis. Similar findings were uncovered in relation to nicotine, a substance like MCH, that play a major role in both energy homeostasis and food reward. We found that blockade of the KOR subtype is not only able to influence the effects of MCH and nicotine on energy homeostasis but also to prevent their effects, exerted at central level, on peripheral lipid homeostasis. This finding has important clinical implications (NAFLD/NASH) whose pharmacological development is being explored [27].

… KEY FINDING 3D: Nicotine acts at the ventromedial nucleus of the hypothalamus to regulate energy expenditure by brown adipose tissue.

We explored mechanisms underpinning the effects of nicotine on weight loss. We found that nicotine-induced weight loss is associated with inactivation of hypothalamic AMPK, decreased orexigenic signalling in the hypothalamus, increased energy expenditure as a result of increased locomotor activity, increased thermogenesis in brown adipose tissue (BAT), and caused alterations in fuel substrate utilization. Conversely, nicotine withdrawal or genetic activation of hypothalamic AMPK in the ventromedial nucleus of the hypothalamus reversed nicotine-induced negative energy balance [28]. In keeping, chronic peripheral nicotine treatment reduced body weight by decreasing food intake and increasing brown adipose tissue thermogenesis in both low fat diet and diet-induced obese (DIO) rats. This overall negative energy balance was associated to decreased activation of hypothalamic

AMP-activated protein kinase in both models. Furthermore, nicotine improved serum lipid profile, decreased insulin serum levels, as well as reduced steatosis, inflammation, and endoplasmic reticulum stress in the liver of DIO rats. We have now added to this knowledge by showing that oestrogen is a key regulator of this VMH AMPK- BAT axis. Dysregulation of this axis could account for changes in energy homeostasis and obesity linked to dysfunction of the female gonadal axis. (SEE SECTION 4E).

… KEY FINDING 3E: Neuropeptides downstream of leptin signalling affect reward circuitry in lateral hypothalamus, NAcc and VTA and enhance motivation for palatable rewards

We linked another key hypothalamic system to food motivation – the melanocortin system (a system targeted by the anorexic hormone, leptin). The melanocortin system includes a subpopulation of neurons in the arcuate nucleus of the hypothalamus that express POMC – this is a large precursor peptide that is cleaved to produce two important neuropeptides – the opioid peptide beta endorphin, and the "melanocortin" alpha melanocyte stimulating hormone (alpha-MSH). Alpha MSH is a potent anorectic (appetite-inhibiting) peptide that acts in the brain through two receptors: the MC3 receptor and the MC4 receptor. Another population of neurons in the arcuate nucleus makes two important neuropeptides that are both potent orexigens – neuropeptide Y and agouti-related peptide (AgRP). AgRP acts at the MC4 receptor to promote food intake. We found that melanocortin signalling in the VTA increases motivation for palatable food via the melanocortin 3 (MC3) receptor. Interestingly, AgRP and neuropeptide Y signalling in the NAcc also increased this motivation [29, 30], and neuropeptide Y also increased motivation when injected into the VTA [29]. Thus different neuropeptide pathways affect different aspects of food-related behaviors, in which motivation can be dissociated from consumption.

…. KEY FINDING 3F: Different neural circuitry is implicated in different aspects of addictive behaviour; the role of the VTA to NAcc projection is especially important for motivated behaviour for a sweet reward, and different neuropeptides specifically modulate addiction-related behaviors.

We examined the role of the VTA to NAcc dopamine pathway in addictive-like behaviours for food, drawing on knowledge from the field of addiction biology that this pathway is important for food-motivated behaviour. While enhanced VTA dopamine tone (previously linked to addiction like behaviour) was as effective for inducing motivated behaviour for food as for cocaine, other addictive-like behaviours were unaffected [31].

…. KEY FINDING 3G: The ventromedial nucleus of the hypothalamus, formerly characterised as the brain's "satiety centre", cannot be a final common pathway for satiety.

There is still little understanding of how appetite-related signals are processed and encoded by hypothalamic neurones under physiological conditions. Our

electrophysiological recordings in an intact, fully integrated system in vivo contribute to this understanding, as we can systematically study neuronal responses to appetite-regulating stimuli administered physiologically and at a range of physiologically relevant concentrations. The ventromedial nucleus of the hypothalamus is a large nucleus which has long been thought to be a satiety centre, but which is also involved in sexual behaviour and aggressive behaviour. Our results with oxytocin and cholecystokinin (CCK, an appetite-inhibiting hormone released from the duodenum) contradict this assumption. The most prevalent response to CCK in the ventromedial nucleus is inhibition; conversely the most prevalent response to oxytocin, a potent appetite-inhibiting neuropeptide, is excitation. Thus these two appetite-inhibiting stimuli have opposite effects on the same neurons at this site, and so it is clear that this cannot be a common pathway for mediating satiety.

We characterised neuronal subpopulations in the ventromedial nucleus by their electrophysiological phenotype and by their expression of a transcription factor, SF1,that is uniquely expressed in the brain at this site. Electrophysiological phenotype predicted responsiveness to CCK and oxytocin, but did not correlate with SF1 expression. The electrophysiological features of these subpopulations indicate a clear pattern of interneuronal coupling, involving a balance of mutual excitation and intrinsically generated activity dependent inhibition. This is interesting, because such an organisation gives rise to a "bistability" of electrical activity – meaning that neurons fire at a high rate or at a low rate with little in between. This in turn indicates that the role of the ventromedial nucleus is in categorical "decision making." It appears now that a key role of the ventromedial nucleus is to regulate the motivation to eat and the motivation for sex in a reciprocal fashion: thus when energy stores are low, food finding is prioritised at the expense of reproduction.

…. KEY FINDING 3H: The supramamillary nucleus of the hypothalamus is potently activated by food reward and by ghrelin.

We conditioned rats to expect to receive a palatable food reward (a small volume of condensed milk) at a certain time of day for one week. After a week, the rats were divided into four groups. The first group received the reward at the expected time; a second group did not receive the reward at the time they were expecting it, a third group received the reward at an unexpected time, and a control group neither expected nor received the reward. We also used rats that had been fed a high-energy palatable diet for five weeks. This overweight group was conditioned in the same way and on the test day all expected the reward but only some received it. In these rats, we mapped the neural pathways that were activated by studying neuronal expression of the immediate-early gene c-fos, a marker for neuronal activation that we have used extensively for mapping neural pathways involved in appetite. In rats receiving the reward, whether they were expecting it or not, we saw a strong activation of the arcuate nucleus (a region strongly associated with homeostatic feeding behaviour). However, we also observed activation in rats that were expecting the reward but did not receive it. This suggests that this region, even during satiety, is involved in signalling receipt of rewarding food and also in reward expectation. In palatable-fed rats there was significantly less activation during expectation of reward suggesting a blunting of reward response after chronic exposure to palatable foods.

In addition, and very unexpectedly we observed strong activation in the hypothalamic supramammillary nucleus (SuM), a brain structure not previously

linked to food intake. We observed moderate activation of the SuM by anticipation or receipt of a predicted reward but very strong activation by receipt of an unexpected reward. We have now shown electrophysiologically that neurons in the SUM are also powerfully activated by systemic administration of ghrelin.

GENERAL OBJECTIVE 4: To establish the importance of "food addiction" as an obesity factor in women, and the mechanistic basis of gender differences in food intake.

… KEY FINDING 4A: Food addiction-related overweight/obesity cannot be identified using anthropometric, metabolic, biochemical or adrenal hormonal parameters

We characterized the anthropometric, metabolic, biochemical and hormonal profile of an overweight/obese group of patients featured by food addiction, defined as the presence of 3 or more symptoms on the Yale Food Addiction Scale questionnaire (YFAS) vs BMI/age matched group with fewer than three symptoms. The two groups did not differ significantly in age, weight, BMI, waist. No significant differences in white blood count, reactive C protein, erythrocyte sedimentation rate, fibrinogen, total and HDL cholesterol, triglycerides, fasting glucose and insulin, glycated hemoglobin, glycaemia and insulin, area under the curve (during Oral Glucose Tolerance Test) were found. Basal ACTH, cortisol and minor adrenal steroids were not different, and there was no difference in diurnal, nocturnal or urinary free cortisol, or in salivary cortisol measured at 7 am and at 11 pm or in the cortisol awakening response (a marker of adrenal axis reactivity).

…KEY FINDING 4B: Multisensory palatable stimulation enhances activation in brain regions involved in reward as well as in those involved in metabolic homeostasis

In Positron Emission Tomography (PET) brain imaging studies, the hypothalamus and midbrain were more activated in food-addicted women than in non-addicted women, and there was an inverse association between the severity of addiction and the activation of the orbitofrontal and prefrontal cortex (involved in inhibitory control). Eleven women (7 food addicted and 4 not food addicted) completed the protocol involving PET scans before and after a three-month period of diet. Weight, BMI and waist circumference were lower after dieting, but comparing the food addicted and non-food addicted women, there was no significant difference in anthropometric, metabolic, biochemical responses to the diet. However, brain activation occurring during multisensory palatable stimulation was reduced more in the food-addicted women, achieving significance in the hypothalamus, midbrain, orbitofrontal, prefrontal, occipital cortices in the food addicted group. Altogether, the data indicate that overweight/obese women showing identical anthropometric and metabolic/hormonal profiles are characterized by a distinct brain pattern of glucose metabolism relating with their food addiction symptoms. Thus, their brain reacts to food sensing and to dieting in a more pronounced fashion than the brain of non-addicted women. The pattern observed in food-addicted women was consistent with a

greater reaction of brain regions to the expected pleasure of consuming palatable foods. The data also suggest that a progressive decline in the response of prefrontal regions may underlie disinhibited overeating, as this decline was significantly associated with a growing number of Yale Food Addiction Scale (YFAS) symptoms in the food-addicted women. Moreover, the diet seems to exert a brain metabolic effect only in the addicted group, whose brain activation during the palatable stimulus seems to normalize to the values measured in the control group. As for other metabolic outcomes, the more affected subjects seem to benefit the most from dietary intervention.

… KEY FINDING 4C: Cerebral positron emission tomography can discriminate between addicted and non-addicted obese/overweight women.

Not addicted and addicted obese/overweight women (identified using the Yale Food Addiction Scale) did not show any difference at the phenotype level. By PET imaging we found that food addiction resulted in a significantly increased activation in the thalamus, hypothalamus, midbrain, putamen, sensory and occipital cortex activation and an inverse association was found between the activation in the orbitofrontal cortex and YFAS score. A three month diet similarly reduced BMI and waist in not addicted and addicted obese/overweight women. The diet seems to exert a brain metabolic effect only in the addicted group, normalizing the brain glucose uptake. Reduction of brain glucose uptake in response to food was not correlated with reduction in body weight, indicating that the effect the intervention on brain metabolism is not (or not only) mediated by the loss of body mass.

… KEY FINDING 4D: In rodents, reward signals in the prefrontal cortex depend on the estrogen environment of the brain.

In studies on rats, we explored the effects of the female sex steroid hormone estradiol on the mesocortical dopamine system. The dopamine pathway from the VTA to the prefrontal cortex contributes to the processing of reward signals, and is regulated by gonadal steroids. We found that estradiol can powerfully modulate the responsiveness of this pathway, increases the expression of key genes related to dopamine neurotransmission and augments the dopamine content of the prefrontal cortex [32]. The findings indicate that reward signals in the prefrontal cortex depend on the estrogen environment of the brain.

… KEY FINDING 4E: In rodents, females are more vulnerable than males to weight gain in response to intermittent sweet treats.

Rats were given, in addition to their normal bland food, intermittent sweet “treats” – sweetened condensed milk, to study how this would affect their total energy intake and weight gain. When the treats had an energy value of about 25% of their total daily intake, male rats compensated reducing their bland food intake, resulting in maintenance of a stable body weight. However, female rats did not compensate fully and increased their body weight when given equivalent rewards. In males, compensation is not due to learning, as treats presented in an irregular and

unpredictable way were still compensated for. The gender difference is quite small but may be sufficient to account over time for substantial weight gain in females. This work links not only to GENERAL OBJECTIVE 6 but also to GENERAL OBJECTIVE 1. However, even in males, compensation is limited - these rats did not reduce their food intake linearly with increasing reward access, so when treats exceeded 60% of average daily intake they started to gain weight. Exactly how the rats compensate for additional energy intake was studied by mapping the neural pathways that are activated when a treat is eaten, and one key pathway that is activated is the hypothalamic oxytocin system: as oxytocin is an anorectic neuropeptide, this is likely to be involved in a reduction of appetite after ingestion of the treat.

See also key finding 3D (Nicotine acts at the ventromedial nucleus of the hypothalamus to regulate energy expenditure by brown adipose tissue): dysregulation of this axis could account for changes in energy homeostasis and obesity linked to dysfunction of the female gonadal axis; key finding 5E: within which we studied the role of estradiol and effects of ghrelin in male and female rats. We found that: 1) Central estradiol (E2) promotes negative energy balance; 2) central E2 increases thermogenic sympathetic nerve activity; 3) Central E2 inhibits AMPK, specifically in the VMH, through ERα; 4) The *VMH AMPK-SNS-BAT axis* mediates the central actions of E2 on energy balance. Furthermore we showed that ghrelin modulates hypothalamic and mesolimbic structures controlling energy balance in both sexes, and that, in females, the estradiol milieu does not influence the ghrelin-induced neuronal activity.

GENERAL OBJECTIVE 5: To study the impact of altered leptin and ghrelin signalling in the mechanisms underlying eating disorders.

Many key findings linked to ghrelin signalling for eating behaviour are already mentioned under objective 3 above, in particular key finding 3A (Ghrelin, a metabolic signal, operates at the neurobiological interface between food intake and addiction) We also showed that oestrogen is a key regulator of the regulation of brown adipose tissue by the ventromedial nucleus of the hypothalamus (see key finding 3B).

… KEY FINDING 5A: Hypothalamic oxytocin neurons are a target for leptin actions

In late pregnancy, all mammals increase their fat stores in anticipation of the metabolic demands of lactation, and this has been thought to involve a desensitisation to the appetite-inhibiting effects of leptin that arises from the steroid environment of pregnancy. This is important to understand, as it suggests that this physiological adaptive process might also underlie the propensity of women for diet-induced obesity. In rodents we showed that one of the hypothalamic targets for leptin is the magnocellular oxytocin system; however we showed that at this site there is little evidence of leptin resistance in pregnancy [33].

… KEY FINDING 5B: Key role of the lateral hypothalamus in leptin resistance

In obese rats, leptin resistance arises in the lateral hypothalamus (a hunger centre involved in homeostatic regulation of appetite, but not in the VTA. We showed that leptin resistance in the lateral hypothalamus regulates body weight and food intake, and that leptin signalling within the lateral hypothalamus is crucial in mediating motivation for sucrose. (Manuscript in preparation).

… KEY FINDING 5C: A novel mechanism by which anorexia may result in amenorrhea.

We identified a new and unexpected target system for ghrelin in the rodent brain, the gonadotropin-releasing hormone (GnRH) network which orchestrates reproduction centrally. We found that GnRH neurons express the ghrelin receptor, and are inhibited by ghrelin administration; this effect involves endocannabinoid retrograde signaling and depends on the estrogen milieu [34]. The results contribute to the better understanding of anorexia nervosa, a severe eating disorder characterized by high level of circulating ghrelin, amenorrhea and severe weight loss.

KEY FINDING 5D. The feeding and food reward effects of ghrelin involve central opioid receptor signalling in addition to pathways linked to dopaminergic, glutamatergic, NPY Y1 and cholinergic signalling.

We explored whether the orexigenic and food reward effects exerted by ghrelin could be mediated by opioid receptors, and obtained clear evidence for a role for both mu-opioid [18] and kappa opioid receptors [26]. We also implicated, amongst others, glutamatergic [15], cholinergic [13] and NPY Y1 [18] signalling pathways in these effects.

Using functional magnetic resonance imaging (fMRI) in rats, we showed that ghrelin regulates both hedonic and homeostatic regulatory centers of feeding in both male and female rats, and studied the role of endocannabinoids and estradiol [35]. We found that ghrelin modulates hypothalamic and mesolimbic structures controlling energy balance in both sexes, and that the endocannabinoid signalling system contributes to ghrelin induced neuronal activity in a region-specific manner. We found that, in females, an estradiol milieu does not influence the ghrelin induced neuronal activity.

GENERAL OBJECTIVE 6: To contribute to a better understanding of the addictive properties of individual food components.

*…. **KEY FINDING 6A: The human brain can detect dietary macronutrients that initiate immediate effects on eating behaviour.***

We explored the effects of macronutrients on food intake, food choices and food preference in humans in a series of studies that involved manipulation of food macronutrients and testing of the effects on gut hormone secretion, food intake and

food preference in lean and obese people. In studies of sucrose preference, we showed that increasing sweetness is associated with increased liking for food, although high sucrose concentrations (60%) were aversive to some people. There were no differences in liking response or total energy intake between lean and obese people. In studies of fat preference, people were offered foods of different fat content that were identical in appearance; we found no difference in the liking scores for the meals, when tested before and after meal consumption. In contrast, in people with heterozygous complete loss of function mutations in the melanocortin 4 receptor gene, MC4R, we observed a higher preference for dietary fat versus sucrose demonstrating that the response to fat in the diet has a strong biological basis.

In lean participants, we compared high sucrose vs sweetener containing meals. Consumption of the isocaloric (high volume) erythritol meal was associated with reduced hunger scores compared to the sucrose control meal. No differences were seen in obese people. Post-prandial plasma glucose and insulin levels were higher after the sucrose control meal than after the erythritol meals, but PYY and GLP-1 responses were similar between the sucrose control and isovolumic erythritol meal in both lean and obese groups. Food intake and sucrose preference during the ad libitum lunch were similar in all conditions in both groups. Thus partial replacement of sucrose by the sweetener erythritol does not attenuate acute behavioural and hormonal parameters of satiety or preference for sucrose in a subsequent ad libitum meal in lean or obese people. These results demonstrate the usefulness of evaluating individual sweeteners, which may interact in unique ways with sweet-taste receptors, vary 1000-fold in sweetness and dosing in food and which may have different absorption kinetics and metabolic fates after consumption.

In studies of high protein vs high fat vs high carbohydrate content meals, we found that PYY levels were highest after the high protein breakfast. GLP-1 levels were highest after the high protein breakfast at 120 min and remained higher throughout the study. These differences did not translate into differences in food intake in lean people.

…. ***KEY FINDING 6B: In rodents, the hypothalamic oxytocin system is promptly and robustly activated by intragastric delivery of high calorific food.***

The finding that the human brain can detect dietary macronutrients that initiate immediate effects on eating behaviour is paralleled by our findings in rodents of neuronal activation and gene expression. In rodents, the direct effects of food ingestion on neuronal activity in the hypothalamus were studied. Intragastric gavage of sweetened condensed milk rapidly and potently activated identified oxytocin cells in the hypothalamus – these neurons are known to have an important appetite-inhibiting role, acting in part on the motivation to eat by the actions of oxytocin at the ventromedial nucleus of the hypothalamus. We identified the brain regions that are activated by release of oxytocin within the brain by mapping expression of the immediate-early gene c-fos after central administration of oxytocin; two sites of strong activation are the amygdala, and the ventromedial nucleus of the hypothalamus.

… KEY FINDING 6C: In humans, calorie restriction affects the sleep/wake cycle.

In a study of changes in energy balance on the sleep/wake cycle, twelve adult male volunteers were studied before and after caloric restriction for 48 h (calorie intake was restricted to 10% of the 24h energy restriction. In the following 48 h, participants were offered a 20 MJ-containing buffet in three meals, and additional snacks that were later weighed. We found that the energy deficit due to caloric restriction was compensated after two days of free feeding. Acute changes in energy balance were reflected in multiple metabolic parameters such as leptin, with a drop to 20% of baseline level after caloric restriction. In free feeding, leptin reverted back to a higher level than at baseline (126%). There was no change in the duration of light sleep and REM sleep, but deep sleep was increased by 18% after caloric restriction and decreased back to baseline levels during free feeding. Interestingly, the increase in deep sleep was entirely due to a marked increase in the duration of stage 4 sleep with no significant difference in stage 3 sleep.

Today's society is exposed to a wealth of palatable high-caloric foods, making overeating and obesity an inevitable consequence. In NeuroFAST we have sought to explore how the brain reward circuitry is affected when exposed to an obesogenic environment. We found that a combination of a fat and sugar diet results in leptin insensitivity and also highlight the role of leptin signalling at the level of the lateral hypothalamus to suppress motivated reward behaviour for palatable foods. Interestingly, we also demonstrated that the post ingestive effects of sucrose (glucose) can be rewarding in nature. We have also assessed the rodent sucrose addiction model at behavioural and molecular levels but find little evidence to support it based on studies in rodents [36].

… KEY FINDING 6D: The obesogenic environment can change food-linked behaviours, including motivated- and binge-like behaviours in rodents but we find little evidence to support "sugar addiction".

Sugar-rich foods are known to engage brain reward systems, which may promote unhealthy eating habits. Sucrose can influence these systems via its sweet taste as well as via its postingestive effects. Indeed, it has previously been shown that the sweet taste and the postingestive effects of sucrose differentially influence its intake and associative learning processes. We investigated the contribution of sweet taste and postingestive effects to incentive motivation. Rats were trained to respond for saccharin (a non-caloric sweetener) or maltodextrin (a carbohydrate with similar postingestive effects as sucrose, but without the sweet taste) and motivation for these solutions was evaluated under a progressive ratio schedule of reinforcement. Initially, the animals responded more for saccharin than for maltodextrin. However, after a learning phase, in which the animals associated the taste of maltodextrin with its postingestive effects, the incentive value of maltodextrin increased compared to saccharin. Although initially, bodyweight was not associated with motivation for either solution, there was an association between body weight and motivation for maltodextrin after the incentive learning phase. Furthermore, maltodextrin, but not saccharin intake was strongly associated with body weight (de Jong, in preparation).

… KEY FINDING 6E: Sweet taste and postingestive effects of food both support motivation for food. The postingestive effects of carbohydrates increase the motivation for food through an incentive learning mechanism.

GENERAL OBJECTIVE 7: To study the effect of workplace stress on eating behaviour, and its mechanistic basis.

We completed extensive food intake and stress measures in the workplace environment, a controlled laboratory experiment and web-tool intervention study in over 750 men and women in the UK, to assess the effect of stress on eating behaviour. This includes detailed measurements on shift workers.

… KEY FINDING 7A: `Stress´ has bi-directional impact on eating behaviour and future interventions need to recognise this if they are to be effective

Stress can influence our health, directly or indirectly through behavioural change. This includes feeding behaviour, specifically the type and quantity of food consumed, where some people will eat more and some people will consume less calories under stress (bi-directional response). We explored in the laboratory setting (and in the free-living setting), that some people over-consume calories when stressed while others under-eat, and how this is linked to individual personality profile and eating behaviour profile. Over-consuming calories when stressed is a risk factor for obesity and diseases including type 2 diabetes and cardiovascular disease, while under-consuming calories is a risk factor in the workplace for performance and wellbeing. Interventions to manage stress in the workplace need to target the right phenotype to result in behaviour change. In our laboratory study of 60 people, 53% consumed more energy when stressed, 43% consumed less energy, and 4% did not change food intake. The energy intake changes were dramatic, at +60% more and -66% less calories consumed, respectively, when stressed, which if continued over several days, would be a significant influence on energy balance and body weight.

- Thirty-two volunteers (mean BMI 25.7 kg/m^2) were classified as 'stress susceptible increase'. They had significantly higher energy intake on the stress test day than on their control day (703 kcal vs 438 kcal).
- Twenty-six (mean BMI 24.6 kg/m^2) were categorised as 'stress susceptible decrease', consuming significantly less on the stress test day (397 kcal vs 604 kcal).
- Two (mean BMI 22.2 kg/m^2) were classified as stress-resistant, their eating behaviour remained unchanged.

These data show that our approach of phenotyping with regard to eating behaviour response (calorie intake when stressed) is a valuable for assessing the type of intervention to apply. If our data had simply been analysed as a group, many of the effects would be missed (and thus initiatives are not likely to target the right people). These data will contribute to evidence base, which strongly suggest that targeting those people who over-eat when stressed, is a valuable means to tackle overweight and obesity, especially in the workplace. Furthermore the group that consume less calories are interesting, as they become anorexic when stressed, which does not put them at risk of obesity related over consumption, but will impact on productivity and concentration, which are other indicators that employers are interested in. This work will provide data for future targeted interventions in the workplace.

… KEY FINDING 7B: Shift-workers consumed less when stressed, whereas day workers consumed more: this has implications for health policy and meal provision in the workplace.

Longitudinal studies have suggested that elevated stress can increase desire for hedonically pleasing, highly palatable energy-dense foods. One in five workers in Europe are employed on shift work involving night work and more than 1 in 20 work extended hours. We recruited emergency responders (fire service & ambulance) and prison staff, all working variable shifts; 93 male and 24 female shift workers with a mean age of 38.7 years and mean BMI of 26.8 kg/m^2. We analysed data using subjects as their own control, to examine variables as 'on shift' v's 'off shift'. Perceived stress was measured using hourly visual analogue scales over 7 days. The shift workers reported elevated stress when on shift compared to off shift, with energy intake (measured by 7-d weighed intake food diary record) and energy expenditure (assessed using an accelerometer) monitored. The shift workers report eating significantly less calories at a meal eating episode when on shift, in comparison to off shift days, which is reflected in significantly higher protein, fat, carbohydrate and alcohol intake when off shift. Unsurprisingly, these subjects were in physically demanding jobs, and thus, physical activity and number of steps were significantly higher when on shift. As we often eat two or more meals a day at work, these data support the ethos that shift workers require access to healthy food to support adequate nutrition and hydration during working hours. Some shift work professions do not have protected break time, which can lead to unhealthy eating styles of snacking or grazing on smaller meals, which tend to be high in energy density. Although these shift workers consumed less and expended more calories on shift, they compensate by consuming calories when off shift, (or even over-compensated), as they did not lose weight over the diary week reporting.

… KEY FINDING 7C: Shift-workers have a detrimental health profile

Working conditions are associated with employees' health behaviour and health, and shift work in particular has been linked to adverse health and unhealthy behaviours including obesity cardiovascular disease, increased snacking, fatigue, sleep and digestive problems, depression, anxiety, disruptions in circadian rhythm and perceived stress. Our studies confirm the detrimental effects of shift work on health. There was more visceral fat (the fat which surrounds the internal organs of the body, and which is particularly associated with a greater risk of diseases such as cardiovascular disease and diabetes) in shift workers than in non-shift workers. There was no significant effect of mean energy intake, stress or total number of daily hassles/week on visceral fat level after controlling for age, BMI and shift pattern. Shift workers worked an average of 46 h/wk significantly more than non-shift workers (40 h/wk). The difference between genders was also significant, with men working an average of 45 h/wk and women 40 h/wk. There were no significant differences in hours worked between age groups. The BMI group corresponding to overweight participants showed most mean hours worked (44 h/wk).

… KEY FINDING 7D: No effect of caffeine consumption on stress

We examined the role of caffeine and stress, as increased caffeine consumption has been related to periods of work-stress, and caffeine influences the neuroendocrine system associated with psychophysiological stress responses. There was a significant relationship between age and caffeine intake, and stress level and caffeine intake, although no significant effects of shift pattern. Additionally, hassle severity (an indicator of stress) affected caffeine intake although there was no effect in relation to number of hassles. The Food Frequency Questionnaires provided complete habitual caffeine intake information from 415 volunteers from different workplaces including shift and non-shift workers. Perceived stress, depression and anxiety levels were measured using the DASS-21 self-reported questionnaire. Additionally, the 'Daily Hassles' Questionnaire measured frequency and severity of daily stressors yielding a greater detail of subjective stressful events. Ordinal regression models controlling for age, gender, BMI and shift pattern were used to determine the relationship between caffeine and stress and stress-related disorders (depression and anxiety). Mean caffeine intake was not significantly different between non-shift workers and shift workers or between men and women, and was not associated with BMI, but was significantly higher in older workers than in those under 45 years 185 vs 157 mg/day). The results showed significant effects of stress and hassle severity, a marginal significant effect of depression, and non-significant effects of anxiety and hassle frequency.

… KEY FINDING 7E: The type of stress is important for the behavioural response.

Daily stressors or hassles are events, thoughts or situations which, when they occur produce negative feelings such as annoyance, irritation, worry or frustration, and/or make you aware that your goals and plans will be more difficult or impossible to achieve. In terms of stress research, the use of daily diaries is becoming more popular, and this is the approach we used, to allow respondents to record temporal changes in day-to-day minor life events or daily stressors/hassles that are part of everyday life and have the advantage of not constraining respondents to a limited number of events. Stressful events are associated with a variety of behavioural responses and generally people use different coping strategies. The foods that have been reported to be over-consumed were snack foods including crisps, chocolate and biscuits. We found significant differences between non-shift and shift workers for $DASS_{21}$ questionnaire stress and anxiety as well as for 'Daily Hassle' frequency and severity. Non-shift workers were more likely than shift workers to have higher levels of perceived stress and anxiety and to rate daily hassles as more frequent and severe. There were non-significant effects of the shift pattern on $DASS_{21}$ depression. An increase in hours worked during the weekend is marginally associated with greater perceived stress.

… KEY FINDING 7F: Workplace interventions need to be evidence-based

When experiencing stress, individuals are more likely to eat high fat and high sugar snacks between meals (e.g. chocolate, crisps, cakes and biscuits) and less likely to eat fruit and vegetables. People who do not maintain a balanced diet are at increased risk of developing heart disease and cancer as they get older. Daily hassles and stressors can be formally broken down to different types of stress: ego-threatening,

interpersonal, work-related, physical and environmental, which were all monitored in the present study. We examined if a public health initiative called Healthy Working Lives, influenced outcomes in indices of stress and food intake.

We recruited public sector workers as follows:

- Workplace 1 comprised staff from Aberdeen College and the University of Aberdeen, with both organisations holding the government initiative Healthy Working Lives
- Workplace 2 secondary schools in Aberdeen and Aberdeenshire with no Healthy Working Lives initiative

We compared workplace 1 and 2, to identify whether the Healthy Working Lives initiative at work is effectively (positively) influencing staff behaviour (eating and physical activity) and stress levels. The two groups were well matched: in Workplace 1 there were 150 subjects (41 male, 109 female) with a mean age of 41 yrs and mean BMI of 25 kg/m^2, and in Workplace 2 there were 155 subjects (42 male, 113 female) with a mean age of 44 yrs and mean BMI of 26 kg/m^2.

We found no major effects of workplace type on the data examined. The HWL initiative does not appear to influence energy intake, energy expenditure, energy balance or stress. We examined total intake and snack intake, and found no significant differences between workplaces. We assessed energy expenditure by accelerometry, and again found no differences between workplaces. We assessed total hours worked and total hours slept, and found no significant differences for age, BMI, gender or Workplace. Five types of daily hassles were identified: Ego-Threatening; Interpersonal; Work-Related; Physical; and Environmental. Ironically, the staff working in the institutions with the Healthy Working Lives initiative report significantly higher stress, reporting more total hassles per day higher total hassles duration per week.

The HWL may have other health benefits (such as smoking cessation or mental health), but the effects on stress and nutritional profile seem limited, from the current dataset. If obesity and unhealthy behaviours are to be discouraged in the workplace, this requires evidence based intervention and robust evaluation. This work highlights the fact that public health initiatives should be evaluated to assess potential health benefits.

… KEY FINDING 7G: Web-based tool is useful to target and influence individual responses to stress

Workplace health and wellness is important, as employee wellbeing is linked to increased productivity and reduced absenteeism, and we have provided evidence that ‘Workplace Wellness’ makes financial sense to reduce modifiable risk factors for non-communicable disease (cardiovascular disease, cancer, type 2 diabetes, chronic lung disease) by creating ‘health-promoting environments,’ In the UK for example, 65% of fire fighters, 30% of office workers and 47% of offshore shift workers are overweight and there is need for evidence based advice for workplace health initiatives.

Our findings suggest that conscientiousness and neuroticism may influence future health status. These influences can be both direct, through facilitating performance of health-enhancing behaviours and/or reducing exposure to daily stressors, and indirect, by buffering the negative effects of stress on health behaviours, and promoting health-enhancing behaviours (such as exercise). These results are

important as they indicate that conscientiousness may have a counterintuitive influence on different types of health behaviours. These small effects are also likely to reflect that the relationships between personality, daily hassles, and health behaviours are influenced by many other variables.

Unfortunately, stress is an inescapable feature of everyday modern life, particularly in the workplace. However, we have shown that a web-based workplace health initiative, can be implemented to provide individual advice, by encouraging behaviour change. This provides an online behaviour change programme based on implementations intentions [37] with remote motivational support to aid the development of healthier lifestyle behaviours. Food intake, stress and body weight can all be individually tracked using this tool in the workplace to allow employees to assess and manage stress. The tool will help people tackle stress, anxiety and depression and related conditions such as weight management for obesity.

The NeuroFAST ROADMAP

At our final meeting, we reflected over current (2015) key gaps in knowledge with a few to the provision of a roadmap beyond this project for future EC research. These are summarized below and we have prepared a flier for circulation of this material (submitted).

NeuroFAST OUTCOME: We provide evidence that subtypes of obesity exist and show that neither being "Food/Eating addicted" nor being "stressed" are consistent determinants of becoming overweight or obese.
FUTURE: If we are to develop personalised strategies for overweight and obesity, future research will need to address why different people respond differently in terms of weight gain to the same environmental stimuli that include stress.

NeuroFAST OUTCOME: We provide a platform for a working definition of the term "Food Addiction" (or "Eating Addiction", as we prefer to describe it). We made progress towards its validation in obese women by brain imaging and also show that being food addicted is not a constant determinant of being overweight/obese.
FUTURE: Further validation and implementation of clinical tools for the diagnosis of "Eating addiction" is warranted – this evidence base is needed to structure policies that guide the environment of those affected and also that provide better health care for those diagnosed.

NEUROFAST OUTCOME: We show that the reward value of food and anticipatory behaviours for it are not only associated with its taste but are also influenced by our gut, exemplified here by the effects of ghrelin on reward behaviour for food.
FUTURE: Appetite-regulating hormones provide a window on brain function for appetite control: by studying their brain mechanism at many levels, we can discover new mechanisms for appetite control – both how much and what we eat.

NeuroFAST OUTCOME: We show that diet impacts on certain food-linked behaviours that can be obesity-promoting but find little evidence to support the idea that the pathways engaged by foods are those that orchestrate addiction-like behaviour.

FUTURE: We need to strengthen behavioural science showing impacts of diet on subsequent choice behaviour for food and the environmental influences involved.

NeuroFAST OUTCOME: Research on causal factors underlying diet induced alterations in energy balance showed that energy-sensors such as AMPK or mTOR are at the core of orchestrating a variety of brain functions (body temperature, energy and metabolic homeostasis) in response to nutritional status and/or diet intake.
FUTURE: As behavioral models in rodents become more sophisticated and can be validated to some extent in a non invasive way in humans it should be feasible to carry out the circuitry analysis linking energy sensors and neuropeptides/ neurotransmitters involved in diet-induced alterations in energy and metabolic homeostasis opening the way for novel clinical approaches to treat obesity and comorbidities.

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