Title: Dopaminergic age-related changes in the anticipatory food reward system in human beings and rats

Name student: Frederike Menage

Supervisors: Prof. dr. U.L.M. Eisel, Prof. dr. G.J. ter Horst & H.R. Hoogeveen, MSc.

Kind of work: Bachelor essay

Dopaminergic age-related changes in the anticipatory food reward system in human beings and rats

Bachelor scriptie Frederike Menage

Supervisors: Prof. dr. U.L.M. Eisel, Prof. dr. G.J. ter Horst & H.R. Hoogeveen, MSc.

Summary

Food choices change during life, which can lead to malnutrition, for example among elderly. In other groups with a changed food choice it is known that the anticipatory food reward system (AFRS) is involved in these changes. This dopaminergic mesolimbic system plays a major role in food choice and is vulnerable to ageing. Because little is known of the age-related changes in humans, in this essay the question is answered what dopaminergic age-related changes are known in rats. Through this more insight can be gained in how the AFRS might change in older adults. A person eats because food is needed to survive. Therefore a person gets reward when food is seen or eaten. Wanting is one aspect of reward that is experienced when food is seen, and with this part of reward the AFRS is active. The VTA, striatum, amygdala, orbitofrontal cortex, parahippocampal gyrus, anterior cingulate gyrus and the fusiform gyrus encompass the AFRS. Changes in activity in these brain areas are shown in people with obesitas or anorexia. It is not known if the AFRS also shows a changed activity in older adults. However, in rats there are known age-related decreases in dopamine (DA) sensitivity or release in all the noticed brain areas except in the anterior cingulate gyrus and the fusiform gyrus. This information makes it more likely to assume that also AFRS in older human adults shows a changed activity.

Content page

Introduction

Healthy ageing is one of the most researched areas these days. Many people want to grow old but healthy. Eating behaviour influences our health. The food choices that people make changes over a lifetime [1a]. It is not alarming that one´s desire for food changes over time since our human body function and cognition is subjected to changes over a life span. What is alarming is the fact that these changes are related to an increased risk for malnutrition, weight loss and decreased quality of life [2].

A study in Brazil showed that 21.7% of the elderly are malnourished [3]. Malnutrition makes older adults vulnerable to influenza virus [4] and through this it can cause weight loss and decreased quality of life. Another study showed that malnutrition in protein intake is a independent risk factor for in-hospital morbidity [5]. Taking together, malnutrition increases the risk of getting sick or a decreased recovery.

Changes in eating behaviour can also be beneficial when people age. A recent study showed that the people who ate healthier were significantly older [6]. Although in this study it is only a five-year difference, it shows that ageing and thereby changes in food choice also can be positive.

Changes in food choice do not happen only among elderly people. Anorexia and obesitas are also disorders related to food choice changes [7,8]. However, the underlying mechanisms of changes in food choice are still largely unknown. The brain plays a central role in behaviour and decision-making. When behaviour is changed, it is likely that the brain also response accordingly. So when food choice changes during life, it is likely that brain activity during this choice also changes. The reward system that is closely related to the anticipation to food is called the anticipatory food reward system (AFRS). The AFRS is a mesolimbic dopaminergic system [9], that becomes activated during the anticipation of food. It was found that individuals with anorexia and obesity show changes in the AFRS. It is up or down regulated in specific regions of this brain circuit [7,8].

The elderly people who are malnourished show, similar to people with obesitas or anorexia, a change in food choice. Until now little is known about anticipatory food reward in relation to ageing. Also why food choice changes during life is still not completely known. The fact that other groups who show food choice changes also show a change in the AFRS, suggests that that this system also changes when people age. Till this far this link stays elusive, there is no evidence for it yet.
To get more insight in the age-related changes in the AFRS, this essay gives an overview of what is known about changes in this area in rats. Through gaining more knowledge in known mechanisms in the brain of rats, a better expectation of the mechanisms in the human brain can be made. The central question of this essay is: what is known about the dopaminergic age-related changes in the AFRS in human beings and rats?

To answer this question, first it has to be known whether the brain plays a role in food choice and which kind of reward behaviours there are in relation to food. To be sure that a changed food choice behaviour has something to do with a changed reward system in the brain, a closer look is given to studies that showed that groups with changed food behaviour also show changes in the reward system of the brain. Then the question can be answered which brain areas are related to this reward system of the brain which is related to food, better known as the AFRS, and what their functions are in this system. Finally, known changes related to the neurotransmitter of the AFRS are given a closer look through an overview of the known age-related dopaminergic changes in the earlier mentioned brain areas of the AFRS in rats. Through this a better expectation can be formed about the age-related changes in AFRS in humans.

1. Regulation of eating-behaviour

Does the brain play a role in eating behaviour?

One of the most essential things in life for organisms is food. Eating food can give an organism reward. According to the Cambridge dictionary, reward means 'something given in exchange for good behaviour or good work'. So in the context of this essay, reward means the good feelings and effects that are experienced when certain behaviour is preformed. When a person gets a reward from something, for example food, he is more willing to work for it. Because the human body needs food, it is not surprising that the human body has reward mechanisms that ensure that we get food.

There are long- and short-term regulations of eating-behaviour. Long-term regulation is the storage or usage of glucose. Especially the storage part in this process is important in the long-term regulation of the body to make sure that there is always enough glucose for the brain. The short-term regulation makes sure that the body gets hungry and is more willing to work for food. First the long-term regulation is discussed, second the short-term regulation. Last the answer to the question why a person is motivated to eat is given.

Long-term regulation of eating-behaviour

Because glucose is an essential energy substrate for the brain [10], the body ensures that there is always glucose available for the brain to function. It stores energy in the body through complex internal regulatory mechanisms. For example the storage of energy in the form of glucose or triglyceride, which is called the anabolic metabolism. This storage process only happens when there is enough energy available, for example when a person is eating. The opposite process, catabolic metabolism, is the breakdown of this glucose or triglyceride to provide energy. This process occurs when there is no energy available out of food (fig 1). A body prefers the state of anabolism. A person gets hungry when it needs more food, so that it doesn't have to breakdown its energy storages (Bear et al. 2007).

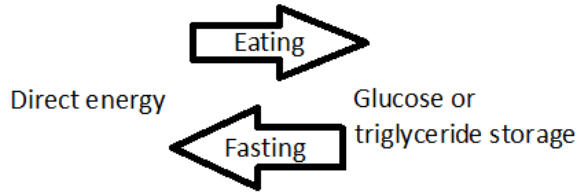

Figure 1: glucose anabolism and catabolism

Like most mechanisms in the body, building up or breaking down glucose is a homeostatic process. After losing or gaining weight, the body will have the urge to return to the old situation, particularly when weight is lost. A hormone that places a major role in this process is leptin [11]. It is released from fat cells (adipocytes). The level of leptin is related to the amount of adipocytes in the body, and the hypothalamus is sensible for an elevated level of leptin. Through interaction with the brain, the body makes sure that it loses weight again through a decreased appetite and a higher energy expenditure. When the body loses weight, the level of leptin is decreased, and through this the body makes sure it gains weight again [1b].

Short-term regulation of eating-behaviour

Like the hormone leptin in long-term regulation of feeding behaviour, the short-term regulation has also hormones who regulate the hunger and satisfied feeling. When a person is hungry ghrelin is released [12,13]. This stimulates neurons that contain NPY and AgRP, and increases a person's appetite and food consumption (fig. 2). When the body is satisfied, cholecystokinin (CCK) inhibits the energy intake [12]. CCK was found in some cells of the intestines, some neurons of the enteric nervous system

and even found in the central nervous system. This shows that body and brain work closely together to regulate feeding behaviour [1b].

Figure 2: overview short-term regulation of eating-behaviour

Motivation to eat

It is generally know that food is essential for living. When food or energy is needed, a person becomes hungry. A hungry person has a big internal motivation to work for food. This motivation is manifested in food seeking behaviour. The motivation to eat is a result of collaboration of hormones released in the body and the response of the brain to this. It may be clear that the brain has a role in eating-behaviour and thus food choice. The next chapter will give an overview of the different parts of reward behaviours related to food, and in which part the AFRS is likely to be involved.

2. Reward behaviour

In which part of reward behaviour is the AFRS involved?

As mentioned previously, in this essay reward is used to mean the desires that are associated with ones' behaviour. When the reward is related to food, there are two kinds of reward behaviours: liking and wanting[9].

Liking

Food is liked when it is pleasurable when it is eaten. The taste and smell are sensed in the body and brain, and the body receives the nutrients of the liked food immediately. It is the hedonic part of reward that activates many cortical areas in the brain [1b]. This part of reward can be tested through facial liking (see fig. 3) [14]. The reward that a human baby or rat experiences when it eats something, is expressed in a characteristic way. When something is liked, it is expressed in a calm satisfied way. A taste that isn't liked is expressed through opening of the mouth. During experiments, the facial expression is a measurement for the amount of reward that is experienced.

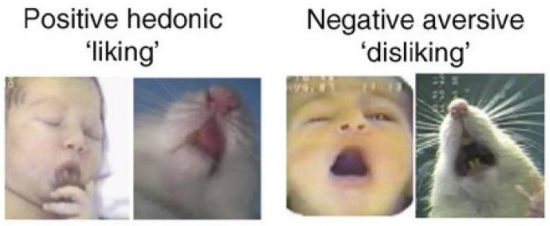

Figure 3: facial liking [14]

Wanting

The other part of reward behavior related to food is wanting, the willingness to work for reward, in this case food. It is an incentive motivation that stimulates approach toward and consumption of reward [14]. When food is seen and wanted, the animal becomes motivated to work to get the desired food. This willingness is initiated by the anticipatory food reward system in the brain. This mediates the anticipation of the body on the food that is seen. In this anticipatory period, the willingness to work for the food, to want the food, becomes bigger.

This part of reward is a mesolimbic-generated process, the AFRS [15]. It is known that rats like the stimulation of the AFRS. Communication between neurons, or stimulation is possible through neurotransmitters. The neurotransmitter of this system is DA [16]. DA is not related to the liking part of reward. When DA neurons are destroyed in the brain, animals still like food, but don't want food anymore [17].

In conclusion, there are two parts in the food reward behaviour - liking and wanting. Wanting plays a role in the motivation to work for food and whereas liking is experienced when food is eaten. So now it is clear that the when the AFRS is active, the reward behaviour that belongs to that is the wanting part. It is likely to assume that when food choice is changed, the wanting reward behaviour is also changed in the brain. This is because through wanting a certain behaviour is acted out or not. To get a better insight in what kind of changes in the AFRS can happen, in the following chapter a closer look is given on what kind of changes in activity people show with a changed food choice.

3. Changes in food-choice behaviour linked to changes in brain activity

Which changes in food-choice behaviour are related to the changes in the AFRS?

Recapitulating what was mentioned earlier, reward plays an important role in behaviour and food choice. Changes in reward experience can influence food choice behaviour. Because the brain plays a central role in reward experience, a change brain activity can affect reward experience and subsequently food choice. Studies have shown that a change in brain activities in the reward system can affect food choice behaviour.

Obesity

One study showed that within obese individuals the individuals who were least successful in losing weight, there was a greater activation in inter alia the anterior cingulated, prefrontal cortex, VTA and the fusiform gyrus [18]. Another study showed that obese women may have a higher motivation to eat than normal weight individuals [19]. Obese people are motivated to work for more food than lean people [20]. Furthermore, obese individuals show greater activation compared to lean individuals when they look at high-calorie foods. This may be caused through a hyperactive reward system. The following parts show greater activation: the orbifrontal cortex, amygdala, ventral striatum, medial prefrontal cortex, anterior cingulated cortex and hippocampus [7]. Overall these studies show that obese individuals show greater activation in areas involved with the AFR when they see high-calorie food. Another study shows that obese people are addicted to food, the availability of DA receptors in the striatum is low and they are less sensible for DA release. To compensate this, they eat more to get the same reward [21].

Anorexia

Another group that shows a changed food choice and a changed AFR are people with anorexia. Independent of the fact whether or not they gained weight, they implicitly wanted high-calorie food less than the healthy control group [22]. When they are seeing pictures of food, they show less activation in the reward system compared to healthy controls [8]. So people who have anorexia show less activity in the AFRS.

Elderly

Changes in the reward system are related to a changed food choice, like the examples that are given before [7,8]. Elderly people also show changes in food choice, which can lead to malnutrition [3]. If the change in food choice behaviour has the same source in elderly as in people with obesitas and anorexia, then it is likely to assume that the reward system is also changed in elderly. Although it is known that the mesolimbic system is particularly vulnerable to ageing [23], it stays elusive whether the reward system is changed in elderly people.

It may be clear that people who show different food choice behaviour, also show a changed activity in the reward system. Obese people show a increased activity [7], people with anorexia a decreased activity [8]. So it is likely to assume that the AFRS is vulnerable to ageing and that in elderly people with a changed food choice this system is changed. Nevertheless, how the changes take place is not clear. The following chapter is going to give more information about the brain areas that are related to the AFRS, and their function in this system.

4. Brain areas related to the AFRS

Which brain areas are related to the AFRS and what functions do they have?

The AFRS is involved in the wanting part of reward. The AFRS is the system that becomes active when a person sees food, without eating it. Which areas are involved in the AFRS and their functions are now explained.

Related areas

The AFRS is a mesolimbic dopaminergic system [9]. The brain areas that are activated when a human being sees sweet food include the dopaminergic midbrain, posterior dorsal amygdala, striatum, ventral tegmental area (VTA), and orbitofrontal cortex are activated [24]. Another study showed that when food is intensely wanted, activity is shown in the parahippocampal gyrus, anterior cingulated and the fusiform gyrus [25] Those brain areas are thought to be related to the AFRS because they show activity when food is seen or thought about, but not eaten.

The neurotransmitter that is involved in this system is DA [16]. So mesolimbic DA transmission mediates the rewarding properties of food and food cues. Animals enjoy it when DA is released in the basal forebrain area, for example in the ventral tegmental area. They are motivated to behave in a way that stimulates the release of DA in this area [1b]. Because DA is released by activation of the AFR system, an animal is more motivated to work for the food that he sees.

Functions of the AFRS brain areas

The activity in all the different brain areas together results in the motivation to work for the food that is seen. To understand better what the specific brain areas are doing in the AFRS, the function of the individual brain area will be described.

The AFRS starts in the VTA, which is located in the midbrain. In this area many mesolimbic DA neurons originate. The axons of those DA neurons go inter alia to the striatum and amygdala [26,27]. DA release in the striatum influences the appetitive aspects of behaviour [28]. The amygdala is besides reward also thought to be related with memory. It can give information about earlier reward that has been experienced [26].

Another area that is related to the AFRS is the orbitofrontal cortex (OFC). This area is involved in decision making in uncertain or unpredictable situations [26]. When not enough information is available about which choice should be made, this area looks to memories of comparable old situations, which hopefully will give more certainty in making the new choice. During the AFR this area maybe gives more information about how to react to the food, if it should be eaten of not. In such a decision attention has to be split over more than one feature of a stimulus, the anterior cingulated gyrus is activated during such a task [29]. This can be one of the reasons why this area is activated during the AFRS.

Many studies say that the fusiform gyrus, a brain area that is also related to the AFRS, reacts strongly and selectively to faces of humans [30]. There is also evidence that this area is used when the viewer looks at similar exemplars of things in which the viewer is specialised, for example cars [31,32]. If human beings are specialised in food, this can be a reason why the fusiform gyrus is activated during the AFR.

The parahippocampal gyrus is also activated. This area is thought to play an important role in relaying information from the hippocampus to areas of the cerebral cortex and the association cortices [33]. The hippocampus is known to be an area that plays an important role in memory. When during the AFR something is wanted, it is likely that this is wanted through memories of the hippocampus. Maybe those memories are reported to other areas in the brain through the parahippocampal gyrus.

Concluding, the AFR is a mesolimbic DA system that becomes active when food is seen that is wanted. During AFR the following brain structures show higher activity: the amygdala, anterior cingulated gyrus, fusiform gyrus, orbitofrontal cortex, parahippocampal gyrus, striatum and the VTA. Now it is clear which areas are involved in the AFRS, finally the dopaminergic age-related changes in those brain areas can be given a closer look.

5. Dopaminergic age-related changes in the AFRS of rats

Which dopaminergic age-related changes are known in the AFRS of rats?

To gain more information in age-related changes in the human AFRS, now an overview is given of the known age-related changes in the brain areas that are related to the AFRS in rats. To be more precise, the dopaminergic age-related changes are going to be discussed. Knowing more about age-related changes in sensitivity or syntheses of DA in the earlier described brain areas which are involved in the AFRS in rats, can give a better understanding or expectation of how the AFRS can be changed in elderly humans. So after described changes in behaviour and overall brain activity which are related to the AFRS, now a closer look is given to dopaminergic age-related changes in the AFRS of rats.

A 24 year old rat is considered aged, cause a two year old rat is comparable with a sixty year old human [34]. First it has to be noted that a decrease in DA is a normal process during aging [35], the amount of DA uptake sites is vulnerable to ageing [36] . Overall aging reduces the activity in the mesocortical DA system [37].

VTA

One study shows that there is no loss of DA neurons in the VTA (in 33 month old rats), but that there is an decrease in neuronal synthetic activity, which can be responsible for the changes in behaviour [38]. Another study shows that in 24 month old rats the level tyrosine hydroxylase, an important enzyme which catalyzes the reaction in which L-DOPA, a precursor of DA, is made, was decreased in the VTA [39]. So the synthesis of DA is decreased, and through the lesser amount of DA that is made, the activity of the AFRS can also be decreased.

Striatum & amygdala

DA concentration are decreased in the striatum and amygdala of 24 month-old rats (fig. 4) [40]. Another study showed that a specific receptor for DA in the amygdala decreases during aging [41]. Reward-responsive neurons in the amygdala are thought to be sensible for change during aging [42]. In addition, the DA levels in the amygdala are higher in younger rats compared to older rats [43].

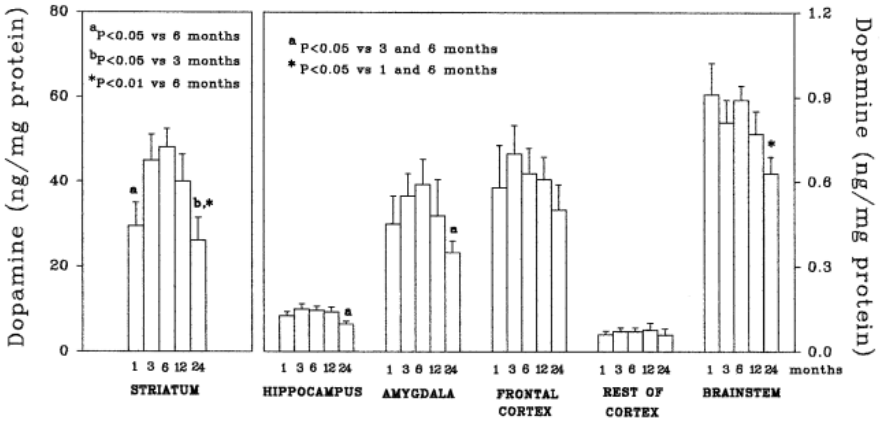

Figure 4: changes with age in levels of DA in several brain areas of the male rat. Values are the main +- SEM of five animals from each group of age (1, 3, 6, 12 or 24-months-old, axix-X). The statistical significance of differences was calculated by one-way ANOVA followed by the Duncan's test. [40]

OFC and parahippocampal gyrus

The OFC is a part of the frontal cortex. Figure 4 shows that DA levels in this area aren't significantly lower. A certain pattern of decrease is shown, but not significant differences. However, it is shown that the OFC is involved in the age-related dopaminergic dysfunction of the cognitive inflexibility development [44]. The hippocampus shows a significance decrease in DA levels and receptors [40,45]. Because the parahippocampal gyrus is related to the hippocampus, a decrease in the hippocampus can also lead to a decrease in the parahippocampal gyrus.
In contrast to the other brain areas that are involved in the AFRS, no facts are known about the influence of ageing on DA in the anterior cingulated gyrus and the fusiform gyrus in rats.

There is a lot known about dopaminergic age-related changes in the AFRS of rats. Most changes are a decrease of sensitivity. So concluding, in rats the sensitivity for DA in the AFRS decreases during life. This makes it more likely to assume that the sensitivity for DA in the human AFRS also will decrease.

6. Conclusion

The focus of this study is to discuss the question: what is known about the dopaminergic age-related changes in the AFRS in human beings and rats?
The brain plays a role in food choice-behaviour, reward behaviours related to food are liking and wanting. The AFRS plays a role in the wanting part of reward behaviour [15]. Groups who show a changed eating-behaviour, like obese persons and people with anorexia, this AFRS shows a changed activity [7,8]. Brain areas that are related to the AFRS are: the amygdala, anterior cingulated gyrus, fusiform gyrus, orbitofrontal cortex, parahippocampal gyrus, striatum and the VTA. The neurotransmitter of the AFRS is DA [16], and in rats most brain areas who are related to the AFRS show a decreased sensitivity or syntheses. So elderly rats are less sensible for reward, or at least show a decreased brain response.

The combination of the facts that in humans with changed food choice, in this case obesitas and anorexia, an altered AFRS is shown, and that rats show a decrease in dopaminergic sensitivity in the AFRS, makes it more likely to assume that in elderly people the activity of the AFRS also decreases.

7. Discussion

The results about the AFRS changes in rats are gained through experiments with different kinds of rats. The variance within those different kinds of rats may influence the results. It should be better if all the results are found in the same kind of rat. Most rat studies are preformed with male-rats, which is good for excluding variance. But the male and female brain and body differ enormously [46,47]. For possible treatments against malnutrition among elderly, both male and female brain has to be understood.

Things that stay elusive are the dopaminergic age-related changes in the anterior cingulated gyrus and the fusiform gyrus. More post-mortem research can be done to the decrease or increase of DA neurons in this area in healthy aged rats.

Also more research has to be done in human beings. In how far the information that is known about changes in the rats are also applicable for humans is discussable. Because they are both mammals, the main brain structures are quite similar. But in how far the mechanisms and for example reward systems are similar is unknown. Human beings also have a ratio, their behaviour is a result of more than only the reward systems. Before they act they can think about the act that they are going to do. This can influence behaviour. In how far rats think before they do something is unknown. Through research in the organisms of interest, the human being self, the most trustworthy answers can be given. This can be done for example through fMRI-studies in which the brain response during a food-choice task is measured, or through post-mortem studies to the amount of DA neurons in the brain areas related to the AFRS. When further research is going to be done to the AFRS in living human beings, it is important that the variable of thinking before acting is excluded. For example, when the subjects have to perform a task, the responding time has to be fast, and they have to act to their first thought or feeling. When a human being thinks about something, also the ratio is going to influence the outcome.

In conclusion, more research has to be done in rats and especially human beings to gain more knowledge in the age-related changes of the AFRS.

8. References

Books:

1a. Shepherd R., Raats M. (2006). *The Psychology of Food Choice.* England: CABI Publishing.

1b. Bear M.F., Connors B.W., Paradiso M.A. (2007). *Neuroscience, exploring the Brain.* Baltimore and Philadelphia: Lippincott Williams & Wilkins.

Articles:

2. VETTA, F., RONZONI, S., TAGLIERI, G. & BOLLEA, M. The impact of malnutrition on the quality of life in the elderly. *Clin. Nutr.* **18,** 259–267 (1999).

3. Cabrera, M. A. S., Mesas, A. E., Garcia, A. R. L. & de Andrade, S. M. Malnutrition and Depression among Community-dwelling Elderly People. *J. Am. Med. Dir. Assoc.* **8,** 582–584 (2007).

4. Chandra, R. K. & Puri, S. Nutritional support improves antibody response to influenza virus vaccine in the elderly. *Br. Med. J. (Clin. Res. Ed).* **291,** 705–6 (1985).

5. Sullivan, D. H. & Walls, R. C. Impact of nutritional status on morbidity in a population of geriatric rehabilitation patients. *J. Am. Geriatr. Soc.* **42,** 471–477 (1994).

6. Swan, E., Bouwman, L., Hiddink, G. J., Aarts, N. & Koelen, M. Profiling healthy eaters: determining factors that predict healthy eating practices amongst dutch adults. *Appetite* **89,** 122–130 (2015).

7. Stoeckel, L. E. *et al.* Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage* **41,** 636–47 (2008).

8. Brooks, S. J. *et al.* Differential neural responses to food images in women with bulimia versus anorexia nervosa. *PLoS One* **6,** e22259 (2011).

9. Castro, D. C. & Berridge, K. C. Advances in the neurobiological bases for food 'liking' versus 'wanting'. *Physiol. Behav.* **136,** 22–30 (2014).

10. Pellerin, L. Food for thought: the importance of glucose and other energy substrates for sustaining brain function under varying levels of activity. *Diabetes Metab.* **36 Suppl 3,** S59–63 (2010).

11. Gibson, L. C. *et al.* Early leptin intervention reverses perturbed energy balance regulating hypothalamic neuropeptides in the pre- and postnatal calorie-restricted female rat offspring. *J. Neurosci. Res.* **93,** 902–12 (2015).

12. Berthoud, H.-R. Vagal and hormonal gut-brain communication: from satiation to satisfaction. *Neurogastroenterol. Motil.* **20 Suppl 1,** 64–72 (2008).

13. Higgins, S. C., Gueorguiev, M. & Korbonits, M. Ghrelin, the peripheral hunger hormone. *Ann. Med.* **39,** 116–36 (2007).

14. Berridge, K. C., Robinson, T. E. & Aldridge, J. W. Dissecting components of reward: 'liking', 'wanting', and learning. *Curr. Opin. Pharmacol.* **9,** 65–73 (2009).

15. Berridge, K. C. 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. *Physiol. Behav.* **97,** 537–50 (2009).

16. Fiorillo, C. D., Tobler, P. N. & Schultz, W. Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* **299,** 1898–902 (2003).

17. Berridge, K. C. & Robinson, T. E. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res. Rev.* **28,** 309–369 (1998).

18. Murdaugh, D. L., Cox, J. E., Cook, E. W. & Weller, R. E. fMRI reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight-loss program. *Neuroimage* **59,** 2709–2721 (2012).

19. Saelens, B. E. & Epstein, L. H. Reinforcing value of food in obese and non-obese women. *Appetite* **27,** 41–50 (1996).

20. Epstein, L. H. *et al.* Food reinforcement, the dopamine D_2 receptor genotype, and energy intake in obese and nonobese humans: Erratum. *Behav. Neurosci.* **122,** 250–250 (2008).

21. Stankowska, A. U. M. & Gjedde, A. Perspective food addiction, caloric restriction, and dopaminergic neurotransmission. *Acta Neuropsychiatr.* **25,** 257–267 (2013).

22. Cowdrey, F. A., Finlayson, G. & Park, R. J. Liking compared with wanting for high- and low-calorie foods in anorexia nervosa: aberrant food reward even after weight restoration. *Am. J. Clin. Nutr.* **97,** 463–70 (2013).

23. Dreher, J.-C., Meyer-Lindenberg, A., Kohn, P. & Berman, K. F. Age-related changes in midbrain dopaminergic regulation of the human reward system. *Proc. Natl. Acad. Sci. U. S. A.* **105,** 15106–11 (2008).

24. O'Doherty, J. P., Deichmann, R., Critchley, H. D. & Dolan, R. J. Neural Responses during Anticipation of a Primary Taste Reward. *Neuron* **33,** 815–826 (2002).

25. Pelchat, M. L., Johnson, A., Chan, R., Valdez, J. & Ragland, J. D. Images of desire: food-craving activation during fMRI. *Neuroimage* **23,** 1486–93 (2004).

26. Adinoff, B. Neurobiologic processes in drug reward and addiction. *Harv. Rev. Psychiatry* **12,** 305–20 (2004).

27. Gardner, E. L. & Ashby, C. R. Heterogeneity of the mesotelencephalic dopamine fibers: physiology and pharmacology. *Neurosci. Biobehav. Rev.* **24,** 115–118 (2000).

28. Robbins, T. W. & Everitt, B. J. Functions of dopamine in the dorsal and ventral striatum. *Semin. Neurosci.* **4,** 119–127 (1992).

29. Corbetta, M., Miezin, F., Dobmeyer, S., Schulman, G. & Petersen, S. SELECTIVE AND DIVIDED ATTENTION DURING VISUAL DISCRIMINATIONS OF SHAPE, COLOR, AND SPEED - FUNCTIONAL-ANATOMY BY POSITRON EMISSION TOMOGRAPHY. *J. Neurosci.* **11,** 2383–2402 (1991).

30. Peelen, M. V & Downing, P. E. Selectivity for the human body in the fusiform gyrus. *J. Neurophysiol.* **93,** 603–8 (2005).

31. Gauthier, I., Skudlarski, P., Gore, J. C. & Anderson, A. W. Expertise for cars and birds recruits brain areas involved in face recognition. *Nat. Neurosci.* **3,** 191–7 (2000).

32. Tarr, M. J. & Gauthier, I. FFA: a flexible fusiform area for subordinate-level visual processing automatized by expertise. *Nat. Neurosci.* **3,** 764–9 (2000).

33. Van Hoesen, G. W. The parahippocampal gyrus: New observations regarding its cortical connections in the monkey. *Trends Neurosci.* **5,** 345–350 (1982).

34. Sengupta, P. The Laboratory Rat: Relating Its Age With Human's. *Int. J. Prev. Med.* **4,** 624–30 (2013).

35. Del Arco, A. *et al.* Prefrontal cortex, caloric restriction and stress during aging: studies on dopamine and acetylcholine release, BDNF and working memory. *Behav. Brain Res.* **216,** 136–45 (2011).

36. Araki, T., Kato, H., Shuto, K., Fujiwara, T. & Itoyama, Y. Effect of aging on dopaminergic receptors and uptake sites in the rat brain studied by receptor autoradiography. *J. Neurol. Sci.* **148,** 131–137 (1997).

37. Segovia, G., Del Arco, A., de Blas, M., Garrido, P. & Mora, F. Effects of an enriched environment on the release of dopamine in the prefrontal cortex produced by stress and on working memory during aging in the awake rat. *Behav. Brain Res.* **187,** 304–11 (2008).

38. Schuligoi, R., Fernandez, J., Heavens, R. P. & Sirinathsinghji, D. J. S. Decreased tyrosine hydroxylase mRNA but not cholecystokinin mRNA in the pars compacta of the substantia nigra and ventral tegmental area of aged rats. *Mol. Brain Res.* **19,** 333–338 (1993).

39. Salvatore, M. Decreased plasma membrane expression of striatal dopamine transporter in aging. *Neurobiol. Aging* **24,** 1147–1154 (2003).

40. Míguez, J. M., Aldegunde, M., Paz-Valiñas, L., Recio, J. & Sánchez-Barceló, E. Selective changes in the contents of noradrenaline, dopamine and serotonin in rat brain areas during aging. *J. Neural Transm.* **106,** 1089–1098 (1999).

41. Small, G. *et al.* D-2 dopamine receptor A1 allele in Alzheimer disease and aging. *Arch. Neurol.* **54,** 281–285 (1997).

42. Roesch, M. R. *et al.* Normal aging alters learning and attention-related teaching signals in basolateral amygdala. *J. Neurosci.* **32,** 13137–44 (2012).

43. Nomura, M., Izaki, Y., Takita, M., Tanaka, J. & Hori, K. Extracellular level of basolateral amygdalar dopamine responding to reversal of appetitive-conditioned discrimination in young and old rats. *Brain Res.* **1018,** 241–6 (2004).

44. Mizoguchi, K., Shoji, H., Tanaka, Y. & Tabira, T. Orbitofrontal dopaminergic dysfunction causes age-related impairment of reversal learning in rats. *Neuroscience* **170,** 1110–9 (2010).

45. Amenta, F. *et al.* Age-related changes of dopamine receptors in the rat hippocampus: a light microscope autoradiography study. *Mech. Ageing Dev.* **122,** 2071–2083 (2001).

46. Scheinost, D. *et al.* Sex differences in normal age trajectories of functional brain networks. *Hum. Brain Mapp.* **36,** 1524–35 (2015).

47. Gur, R. *et al.* Sex differences in brain gray and white matter in healthy young adults: Correlations with cognitive performance. *J. Neurosci.* **19,** 4065–4072 (1999).