Role of orexin and opioid dynorphin peptides in obesity behavioral dysregulation

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Food-seeking behavior and uncertainty

Uncertainty can be understood as a measure of the expectation of the reward prediction error in a given environment. This measure of the difference between expected reward and current reward is encoded by dopamine neurons (Bayer and Glimcher 2005). Furthermore, this system can modify decision-making policies based on the reward-prediction error (Pessiglione et al. 2006). Food-seeking behavior can be conceptualized as series of decision-making actions occurring in an environment with varying grades of uncertainty, where the reward prediction error evaluates each feeding bout, and over a history of bouts, uncertainty over environment rewards is obtained.

Environment uncertainty and food intake

Under higher uncertainty levels of environment food disposition, animal food-seeking bouts are increased, resulting in hoarding-type behavior, arguably a mechanism to prevent possible starvation (Anselme and Güntürkün 2019). However, this behavior can also be explained by food scarcity or insufficient energetic supply by the environment. The latter case does not necessarily predict uncertainty as this can be high on average, but volatile from time to time. Nevertheless, when constant food position changes alter feeding environment, an increased intake is observed (Forkman 1993), so food access variability can trigger, by itself, an increased food-seeking behavior. Sign-tracking also increases when uncertainty about reward probabilities also increases (Anselme, Robinson, and Berridge 2013). That is, motivation is increased under the uncertainty of reward delivery. In addition to modifying intake, uncertainty levels can affect energy expenditure (Bednekoff and Houston 1994), even when overall food levels are equated in predictable and unpredictable setting (Cuthill 2000).

Uncertainty representations at neural level

If uncertainty can modulate food-seeking behavior in order to increase intake and better sustain energetic reserves. It is expected to have at least, to functional instances (1) a uncertainty sensing unit and (2) a reward processing unit, which can relay information to homeostatic-related and decision-making loci, to integrate such information a determine

the next action to take. In humans such functional instances seems to be separated, where nucleus accumbens, thalamus and medial orbitofrontal cortex are more activated in unpredictable reward scenarios, and predictable scenarios with right superior temporal gyrus (Tanaka et al. 2006). Task-related brain activity is reduced in more predictable environments, likely by lowering mean prediction error, however, anterior cingulate cortex (ACC), shows augmented activation when predictability drops (Davis, Choi, and Benoit 2010). When situated in a learning task, ventral striatum has been related to short-term reward prediction, whereas dorsal striatum was related with long-term reward prediction (Tanaka et al. 2006).

Short-term reward prediction is closely related to uncertain environments as immediate rewards don't provide any information about subsequent rewards, which is the opposite case of certain (or regular) environments, where each rewards provide all information to predict the next reward. Direct tracking of environment volatility shows that this is well represented in ACC, moreover, this ACC activity is modulated by volatility when reward is observed after an action is made, so the observed effect might imply a modulation of value assigned to the outcome given environment uncertainty (Behrens et al. 2007).

When representing uncertainty of a given environment, an agent must pair the value obtained with the action performed. For each action possible the agent updates the value of action-reward based on the reward prediction error. The objective of the agent is to minimize the reward-prediction error. Thus, the uncertainty of a given environment is represented by the time taken, for a given agent, to converge into action-rewards value that minimize reward-prediction error. Such action-reward pairing at cue presentation time has been found to be represented at the putamen, whereas reward-prediction error in the caudate nucleus when feedback is presented (Haruno and Kawato 2006).

It can be inferred from the way action-reward pairing is stated, that it corresponds to action selection based on a history of reward which are mediated by the reward prediction error. Inhibition of putamen activity has effectively shown a reduction in performance when the task requires the consideration of reward history to select actions (Muranishi et al. 2011). Signal encoding, however, seems to be more complex as basal ganglia direct pathway encode rewards outcomes and indirect pathway represented the next-action selection (Nonomura et al. 2018).

Models explaining food intake in obesity

Reinforcement learning models

Temporal-difference learning models, state how agents can estimate reward values in uncertain environments. At each time-step, the agent computes de value of a given state considering (1) the estimated value (randomly initiated at first) and (2) the temporal-difference error which state the distance between the estimate of state value and the actual

reward obtained in such state.

$$V(S_t) \leftarrow V(S_t) + \alpha(Temporal\ Difference\ Error) \qquad (1)$$

$V(S_t)$ denotes the estimated value at a given state, and α is used to model the agent learning rate, that is, the rate at which state value is updated, and thus able to affect agent behavior. Additional parameter ρ has been proposed to model sensitivity to reward (Huys et al. 2013; Kroemer and Small 2016), such that the temporal difference error accounts for the subjective value of obtained rewards.

$$Temporal\ Difference\ Error = \rho \times Reward - V(S_t) \qquad (2)$$

Obese subjects had shown reduced dorsal striatum activity to food rewards, which has been interpreted as reduced pleasure for food. However, simulations under previously presented model show another option, that is, obese subject show heightened reward sensitivity but decreased learning rates, ending in a lowered state value estimation (Kroemer and Small 2016). Modeled learning rates measures, had shown that this is the case in obese subjects, moreover, it pointed that negative prediction errors (equivalent of temporal difference error) were used to a lesser extent than lean subjects, whereas positive errors showed no differences (Mathar et al. 2017). This points to a difficulty to update reward or state values when the estimated reward is higher than the actual reward, possibly reflecting a short-term reward estimation.

It should be noted that more recent neuroimaging evidence point in favor of a hyper-reactivity of rewards circuitry instead of hypo-reactivity, however, conclusions obtained by the model still holds, as such hyper-reactivity, is accompanied by a bias to immediate rewards (Stice and Burger 2019). In line with the reinforcement learning model presented, evidence from probabilistic learning paradigm in obese subjects, shows a decrease impact of negatively valued choices on consequent behavioral adaptation (Kube et al. 2018). This seemingly opposing results can stem from, previously not considered, quadratic associations between BMI and reward sensitivity, where an inverted U-shape is observed and BMI increases (Horstmann, Fenske, and Hankir 2015).

Basic reinforcement learning models presented here provide a useful framework to assess the impact of (1) reward sensitivity, (2) learning rates and (3) reward prediction error, more complex models can consider stay/leave behaviors (Kroemer et al. 2019), which are part of concurrent decision making. As such, obesity behavior can be characterized for concurrent choices, however, another interesting dimension is decision across different time spans.

Delayed discouting models

Although the factor determining obesity as an outcome are multiple (Ang et al. 2013), it is reasonable to assume that the more immediate cause is excess intake relative to energetic demands. Moreover, excess of intake is determined in a instance to instance basis, where a decision considering short and long-term benefits/risk must be made. With this in consideration, one can assume that obesity, in part, is caused by sub-optimal short/long-term benefit/risk assessments when taking feeding decisions. If this was the case, as previously noted, areas that are related to compute options value in the short/long term, such as the ACC should be in someway impaired.

Delayed discouting referers to the depreciation of a certain reward as function of the time required to obtain it (da Matta, Gonçalves, and Bizarro 2012), as such, it provides a measures of how reward-related systems bias decision to short or long term. Obese subjects show a robust tendency to steeply discount future rewards (Amlung et al. 2016), thus, favoring short-term rewards.

Furthermore, ACC, among other structures, shows relative atrophy in obese subjects (Wang et al. 2017; Raji et al. 2009), suggesting an impairment of the previously mentioned functions. This findings can be interpreted as if an impairment in environment uncertainty assessment results in a preference for short-term rewards. If this were the case, palatable food sensory cues, which trigger food-intake, would dominate over more, long-term modulated, decisions, such as healthy food intake (Higgs 2016).

Higher future rewards discounting paired with increased motivation to work for food, predict higher caloric intake (Rollins, Dearing, and Epstein 2010), and this effect seems to hold even for low energy-density food (Epstein et al. 2014). The rate of reward discouting, thus, informs about the predisposition to increased energetic intake, independent of possible food-property related effects. Similar effects has been found in children (Best et al. 2012) but not in adult males (Smulders, Boswell, and Henderson 2019). Moreover, this effects seem to be directly related to body fat (Rasmussen, Lawyer, and Reilly 2010).

Orexin/Hypocretin system control of foraging

Up to this point, the way reward-related systems interact with environment uncertainty has been discussed. Several structures seem to be involved in integrating reward value in face of environment volatility. Moreover, empirical findings of food-seeking behavior in predictable/unpredictable environments were pointed, however, the direct mechanism that guides food-seeking behavior is lacking. One such system is the Orexin/Hypocretin (HO), which is part of energy homeostatic and feeding pathways (Toshinai et al. 2003), and plays a large role in increasing food intake (Wolf 2009). However, a more broad and complex opioid system is thought to control food intake, which in turn is modulated by food preference and selective to certain macro-nutrients, such as fat (Taha 2010). More

recent evidence has linked the activation of hypothalamic HO system to an increase in short-term spatial memory, which is a function that supports exploratory foraging behavior (Aitta-aho et al. 2016).

Moreover, orexin promotion of such foraging-related behavior has been postulated as one of its main functions (Barson 2020). Such function is relevant because foraging behavior evolved in a specific type of environment, where resources are sparse, clustered and in potential risk of predation, and developed relatively stable strategies to deal with such conditions (Wosniack et al. 2017). Thus, foraging behavior, seeks to generate a strategy to maximize energetic intake in a partially known environment, however, if environment resource are non-depleting it can lead to behaviors such as binge eating, finally resulting in excess caloric intake (Barson 2020).

To provide a connection between food-seeking behavior and uncertainty, evidence on the effects of increasing such uncertainty on the proximal effect of food-seeking behavior, that is, food intake, is neccessary. In that regard, it was pointed that, possibly because of survival mechanisms, environment uncertainty increased food intake and reduced energetic spending. Then, the sufficient functions to support such findings were discussed, emphasizing related structures and functions associated with each on to be accounted by problems with delayed-discounting and ACC atrophy, which points towards a sub-optimal pairing between reward value assignment given environment uncertainty levels. Also, OH system role in foraging was discussed as a proximal cause of overfeeding. Together, this suggests that food-seeking behavior evolved to provide optimal decision-making strategies in uncertain and scarce environments, however, (1) when environment energetic density is high, such strategies would result in overfeeding and (2) obesity in itself can impair homeostatic regulation by altering structures related to uncertainty and reward value processing. Previous points, predict that underlying foraging mechanisms, in certain environments, can lead to obesity.

Obesogenic environments

Cafeteria diet and uncertainty

The decision making problem in obesity

Conclusions

References

Aitta-aho, Teemu, Elpiniki Pappa, Denis Burdakov, and John Apergis-Schoute. 2016. "Cellular Activation of Hypothalamic Hypocretin/Orexin Neurons Facilitates Short-

Term Spatial Memory in Mice." *Neurobiology of Learning and Memory* 136 (December): 183–88. https://doi.org/10.1016/j.nlm.2016.10.005.

Amlung, M., T. Petker, J. Jackson, I. Balodis, and J. MacKillop. 2016. "Steep Discounting of Delayed Monetary and Food Rewards in Obesity: A Meta-Analysis." *Psychological Medicine* 46 (11): 2423–34. https://doi.org/10.1017/S0033291716000866.

Ang, Yeow Nyin, Bee Suan Wee, Bee Koon Poh, and Mohd Noor Ismail. 2013. "Multifactorial Influences of Childhood Obesity." *Current Obesity Reports* 2 (1): 10–22. https://doi.org/10.1007/s13679-012-0042-7.

Anselme, Patrick, and Onur Güntürkün. 2019. "How Foraging Works: Uncertainty Magnifies Food-Seeking Motivation." *Behavioral and Brain Sciences* 42: e35. https://doi.org/10.1017/S0140525X18000948.

Anselme, Patrick, Mike J. F. Robinson, and Kent C. Berridge. 2013. "Reward Uncertainty Enhances Incentive Salience Attribution as Sign-Tracking." *Behavioural Brain Research* 238 (February): 53–61. https://doi.org/10.1016/j.bbr.2012.10.006.

Barson, Jessica R. 2020. "Orexin/Hypocretin and Dysregulated Eating: Promotion of Foraging Behavior." *Brain Research* 1731 (March): 145915. https://doi.org/10.1016/j.brainres.2018.08.018.

Bayer, Hannah M., and Paul W. Glimcher. 2005. "Midbrain Dopamine Neurons Encode a Quantitative Reward Prediction Error Signal." *Neuron* 47 (1): 129–41. https://doi.org/10.1016/j.neuron.2005.05.020.

Bednekoff, Peter A., and Alasdair I. Houston. 1994. "Avian Daily Foraging Patterns: Effects of Digestive Constraints and Variability." *Evolutionary Ecology* 8 (1): 36–52. https://doi.org/10.1007/BF01237664.

Behrens, Timothy E J, Mark W Woolrich, Mark E Walton, and Matthew F S Rushworth. 2007. "Learning the Value of Information in an Uncertain World." *Nature Neuroscience* 10 (9): 1214–21. https://doi.org/10.1038/nn1954.

Best, John R., Kelly R. Theim, Dana M. Gredysa, Richard I. Stein, R. Robinson Welch, Brian E. Saelens, Michael G. Perri, Kenneth B. Schechtman, Leonard H. Epstein, and Denise E. Wilfley. 2012. "Behavioral Economic Predictors of Overweight Children's Weight Loss." *Journal of Consulting and Clinical Psychology* 80 (6): 1086–96. https://doi.org/10.1037/a0029827.

Cuthill, I. C. 2000. "Body Mass Regulation in Response to Changes in Feeding Predictability and Overnight Energy Expenditure." *Behavioral Ecology* 11 (2): 189–95. https://doi.org/10.1093/beheco/11.2.189.

da Matta, Adriana, Fábio Leyser Gonçalves, and Lisiane Bizarro. 2012. "Delay Discounting: Concepts and Measures." *Psychology & Neuroscience* 5 (2): 135–46. https://doi.org/

10.3922/j.psns.2012.2.03.

Davis, Jon F., Derrick L. Choi, and Stephen C. Benoit. 2010. "Insulin, Leptin and Reward." *Trends in Endocrinology & Metabolism* 21 (2): 68–74. https://doi.org/10.1016/j.tem.2009.08.004.

Epstein, Leonard H., Noelle Jankowiak, Kelly D. Fletcher, Katelyn A. Carr, Chantal Nederkoorn, Hollie A. Raynor, and Eric Finkelstein. 2014. "Women Who Are Motivated to Eat and Discount the Future Are More Obese: BMI and Reinforcement Pathology." *Obesity* 22 (6): 1394–9. https://doi.org/10.1002/oby.20661.

Forkman, B. A. 1993. "The Effect of Uncertainty on the Food Intake of the Mongolian Gerbil." *Behaviour* 124 (3-4): 197–206. https://doi.org/10.1163/156853993X00579.

Haruno, Masahiko, and Mitsuo Kawato. 2006. "Different Neural Correlates of Reward Expectation and Reward Expectation Error in the Putamen and Caudate Nucleus During Stimulus-Action-Reward Association Learning." *Journal of Neurophysiology* 95 (2): 948–59. https://doi.org/10.1152/jn.00382.2005.

Higgs, Suzanne. 2016. "Cognitive Processing of Food Rewards." *Appetite* 104 (September): 10–17. https://doi.org/10.1016/j.appet.2015.10.003.

Horstmann, A., W. K. Fenske, and M. K. Hankir. 2015. "Argument for a Non-Linear Relationship Between Severity of Human Obesity and Dopaminergic Tone: Relationship Between Obesity and Dopaminergic Tone." *Obesity Reviews* 16 (10): 821–30. https://doi.org/10.1111/obr.12303.

Huys, Quentin JM, Diego A Pizzagalli, Ryan Bogdan, and Peter Dayan. 2013. "Mapping Anhedonia onto Reinforcement Learning: A Behavioural Meta-Analysis." *Biology of Mood & Anxiety Disorders* 3 (1): 12. https://doi.org/10.1186/2045-5380-3-12.

Kroemer, Nils B., Ying Lee, Shakoor Pooseh, Ben Eppinger, Thomas Goschke, and Michael N. Smolka. 2019. "L-DOPA Reduces Model-Free Control of Behavior by Attenuating the Transfer of Value to Action." *NeuroImage* 186 (February): 113–25. https://doi.org/10.1016/j.neuroimage.2018.10.075.

Kroemer, Nils B., and Dana M. Small. 2016. "Fuel Not Fun: Reinterpreting Attenuated Brain Responses to Reward in Obesity." *Physiology & Behavior* 162 (August): 37–45. https://doi.org/10.1016/j.physbeh.2016.04.020.

Kube, Jana, David Mathar, Annette Horstmann, Sonja A. Kotz, Arno Villringer, and Jane Neumann. 2018. "Altered Monetary Loss Processing and Reinforcement-Based Learning in Individuals with Obesity." *Brain Imaging and Behavior* 12 (5): 1431–49. https://doi.org/10.1007/s11682-017-9786-8.

Mathar, David, Jane Neumann, Arno Villringer, and Annette Horstmann. 2017. "Failing to Learn from Negative Prediction Errors: Obesity Is Associated with Alterations in

a Fundamental Neural Learning Mechanism." *Cortex* 95 (October): 222–37. https://doi.org/10.1016/j.cortex.2017.08.022.

Muranishi, Manabu, Hitoshi Inokawa, Hiroshi Yamada, Yasumasa Ueda, Naoyuki Matsumoto, Masanori Nakagawa, and Minoru Kimura. 2011. "Inactivation of the Putamen Selectively Impairs Reward History-Based Action Selection." *Experimental Brain Research* 209 (2): 235–46. https://doi.org/10.1007/s00221-011-2545-y.

Nonomura, Satoshi, Kayo Nishizawa, Yutaka Sakai, Yasuo Kawaguchi, Shigeki Kato, Motokazu Uchigashima, Masahiko Watanabe, et al. 2018. "Monitoring and Updating of Action Selection for Goal-Directed Behavior Through the Striatal Direct and Indirect Pathways." *Neuron* 99 (6): 1302–1314.e5. https://doi.org/10.1016/j.neuron.2018.08.002.

Pessiglione, Mathias, Ben Seymour, Guillaume Flandin, Raymond J. Dolan, and Chris D. Frith. 2006. "Dopamine-Dependent Prediction Errors Underpin Reward-Seeking Behaviour in Humans." *Nature* 442 (7106): 1042–5. https://doi.org/10.1038/nature05051.

Raji, Cyrus A., April J. Ho, Neelroop N. Parikshak, James T. Becker, Oscar L. Lopez, Lewis H. Kuller, Xue Hua, Alex D. Leow, Arthur W. Toga, and Paul M. Thompson. 2009. "Brain Structure and Obesity." *Human Brain Mapping*, NA–NA. https://doi.org/10.1002/hbm.20870.

Rasmussen, Erin B., Steven R. Lawyer, and William Reilly. 2010. "Percent Body Fat Is Related to Delay and Probability Discounting for Food in Humans." *Behavioural Processes* 83 (1): 23–30. https://doi.org/10.1016/j.beproc.2009.09.001.

Rollins, Brandi Y., Kelly K. Dearing, and Leonard H. Epstein. 2010. "Delay Discounting Moderates the Effect of Food Reinforcement on Energy Intake Among Non-Obese Women." *Appetite* 55 (3): 420–25. https://doi.org/10.1016/j.appet.2010.07.014.

Smulders, Tom V., Timothy Boswell, and Lindsay J. Henderson. 2019. " 'How Foraging Works': Let's Not Forget the Physiological Mechanisms of Energy Balance." *Behavioral and Brain Sciences* 42: e51. https://doi.org/10.1017/S0140525X1800198X.

Stice, Eric, and Kyle Burger. 2019. "Neural Vulnerability Factors for Obesity." *Clinical Psychology Review* 68 (March): 38–53. https://doi.org/10.1016/j.cpr.2018.12.002.

Taha, Sharif A. 2010. "Preference or Fat? Revisiting Opioid Effects on Food Intake." *Physiology & Behavior* 100 (5): 429–37. https://doi.org/10.1016/j.physbeh.2010.02.027.

Tanaka, Saori C., Kazuyuki Samejima, Go Okada, Kazutaka Ueda, Yasumasa Okamoto, Shigeto Yamawaki, and Kenji Doya. 2006. "Brain Mechanism of Reward Prediction Under Predictable and Unpredictable Environmental Dynamics." *Neural Networks* 19

(8): 1233–41. https://doi.org/10.1016/j.neunet.2006.05.039.

Toshinai, Koji, Yukari Date, Noboru Murakami, Mitsushi Shimada, Muhtashan S. Mondal, Takuya Shimbara, Jian-Lian Guan, et al. 2003. "Ghrelin-Induced Food Intake Is Mediated via the Orexin Pathway." *Endocrinology* 144 (4): 1506–12. https://doi.org/10.1210/en.2002-220788.

Wang, Haifeng, Baohong Wen, Jingliang Cheng, and Hongpeng Li. 2017. "Brain Structural Differences Between Normal and Obese Adults and Their Links with Lack of Perseverance, Negative Urgency, and Sensation Seeking." *Scientific Reports* 7 (1): 40595. https://doi.org/10.1038/srep40595.

Wolf, George. 2009. "Orexins: A Newly Discovered Family of Hypothalamic Regulators of Food Intake." *Nutrition Reviews* 56 (6): 172–73. https://doi.org/10.1111/j.1753-4887.1998.tb06131.x.

Wosniack, Marina E., Marcos C. Santos, Ernesto P. Raposo, Gandhi M. Viswanathan, and Marcos G. E. da Luz. 2017. "The Evolutionary Origins of Lévy Walk Foraging." Edited by Frederic Bartumeus. *PLOS Computational Biology* 13 (10): e1005774. https://doi.org/10.1371/journal.pcbi.1005774.