

Theoretical and empirical framework

The natural setting for food-seeking behavior

Foraging comprises the complete set of activities and behaviors related to obtaining food in a wild environment. Food-seeking behavior is a particular element of such a set, including all re-orientation and locomotion activity related to the obtention of food. Thus, food-seeking behavior considers up to food encounter, whereas foraging behavior is still present in future utilization of acquired energy, including feeding or possibly hoarding (Kramer 2001).

The food-seeking phase of foraging must ensure an optimal way to acquire food using the least amount of resources and reduce exposure to potential predators. If the food-resources location were static, food-seeking behavior only necessary input would be an initial sampling of the environment and then matching landscape cues. This is not the case. Animals do not necessarily follow landscape cues (Bartumeus et al. 2016), or even develop search strategies based on them (Kölzsch et al. 2015). Moreover, animals are subject to incomplete knowledge about resource location, quality, and probability of obtention (G. H. Pyke 1984). Thus a foraging animal must determine its food-seeking behavior considering an inherently stochastic environment with only partial knowledge.

In a stochastic environment, to establish optimal food-seeking strategies, animals should consider the overall statistical properties of the environment. Otherwise, local environment volatility could lead to the misguided preference for lower mean quality food resources with high variability, leading to starvation in the long run. Empirical evidence has shown that multiple animal species, including humans, perform searching in a Lévy-walk fashion (Garg and Kello 2021; A. Reynolds et al. 2018; Viswanathan et al. 1996; Kölzsch et al. 2015). Lévy-walks are random walks with a Lévy distribution, which produces heavy-tails and describes multiple concentrated movements with sharp turning angles followed by few ballistic displacements; such patterns produce optimal searches in various environments with dispersed resources in a patchy-fashion (Wosniack et al. 2017). Although its generative mechanism is not precise (A. Reynolds et al. 2018) there is evidence that this mechanism is partially independent of sensory information (Humphries and Sims 2014; Sims et al. 2019), probably selected through evolution as it optimizes food searching with partial or complete lack of knowledge (Wosniack et al. 2017).

Given that these food-seeking strategies are present without sensory information and are ubiquitous in animals, food-seeking behavior probably evolved to deal with partial knowledge in an uncertain environment. While Lévy-walks provide a ‘basal’ strategy when there is partial or no knowledge, upon food encounter, the search strategy switches to a more focused one similar to Brownian-motion (A. M. Reynolds and Frye 2007; Nauta, Khaluf, and Simoens 2020). Furthermore, computational modeling points out how this switch between informed (Brownian-like) and random search might depend on food encounter uncertainty

(Anselme, Otto, and Güntürkün 2017). Together this data suggests that animal’s food-seeking behavior evolved to deal with uncertain environments and partial knowledge. Moreover, environment uncertainty itself modulates the baseline strategy, optimally searching for food even when knowledge is not complete.

Foraging and uncertainty

Specific food-seeking strategies, such as the Lévy-Walks, emerge from the animal’s irreducible uncertainty when foraging. Uncertainty then informs food-seeking behavior. However, how animals capture or process this uncertainty while searching for food has not yet been explained; such is the aim of this section.

If an animal performs any food-seeking strategy in a specific area of the environment, there is a probability of success, depending on resource density and the specific strategy. With a fixed strategy, resource density determines the probability. Moreover, as the resource density changes over time, so does the probability of successfully obtaining food. Moreover, in conjunction with limited perceptual abilities (Bartumeus et al. 2016), the environment appears as being of stochastic nature (Caraco et al. 1990).

An animal that does not consider environment stochastic nature in its food-seeking behavior will act greedily upon sampled values. Acting greedily implies that the animal will always choose the option that yielded the most values in an initial random sampling. Thus, acting greedily is analogous to neglecting that the sample comes from a stochastic distribution of rewards. This is problematic as it makes food-seeking strategy insensitive to reward variation (Sutton and Barto 2018). One could relax this assumption and propose that animals act upon the mean rewards, such as the classical model by Charnov (1976), which determines the strategy based on the current patch value against the global mean of the environment. Nevertheless, such rule-based models do not provide good fit to behavioral data (Nonacs 2001; Le Heron et al. 2020; G. H. Pyke 2010; Hayden, Pearson, and Platt 2011).

The competing models to rule-based ones are those which effectively consider uncertainty into its formulation. However, for this to make biological sense, animals should be able to track uncertainty measures precisely. Risk considers the spread of possible outcomes, or similarly, the standard deviation of the expected outcome (Rothwell and Stock 1988). In humans, the anterior cingulate cortex (ACC) tracks risk (Christopoulos et al. 2009). Moreover, ACC tracks risk in a context-dependent fashion; that is, it considers cue-related information to determine the risk and expected value of a given option (van Holstein and Floresco 2020). While risk is the component of uncertainty that measures the spread of outcome, volatility signifies how often an environment changes its contingencies, for example, in the action and outcome probability pairing. In learning tasks, volatility increases ACC activity (Behrens et al. 2007). The main goal of tracking uncertainty is to augment the chance of success while searching for food. In that regard, filtering out uncertainty regarding outcomes

can prove beneficial as the actual outcome prediction does not become affected by noise. Stolyarova and Izquierdo (2017) showed that rats could optimally choose options with more significant value (mean reward waiting time) despite large associated variability. Furthermore, lesions in the orbitofrontal cortex (OFC) showed an impaired ability to change preference when the mean rewards were up or downshifted; that is, value inference became noisy.

All previously mentioned aspects of uncertainty can be categorized within the notion of expected and unexpected uncertainty. Yu and Dayan (2005) proposed expected uncertainty as the uncertainty regarding outcomes when contingencies (outcome given a particular action) remain stable but are subject to some noise. In contrast, unexpected uncertainty represents a drastic change in the contingencies that likely reflects a structural change in the environment. For example, Stolyarova and Izquierdo (2017) experiment measured rat behavioral modulation with expected uncertainty, and Behrens et al. (2007) showed ACC activity increases in the case of unexpected uncertainty. Considering both kinds of uncertainties enables the animal to balance top-down and bottom-up information if the obtained rewards present some variation is should not modify learned contingencies that maps actions with rewards in a given environment, so top-down control should dominate bottom-up input. On the other hand, if obtained rewards present a large amount of variation, the balance should switch in order to prioritize bottom-up input to increase learning about new contingencies (Yu and Dayan 2005; Soltani and Izquierdo 2019).

Yu and Dayan (2005) dual notion of uncertainty can be considered in terms of stationary and non-stationary environments. A non-stationary environment is one where the outcome variance remains unchanged, whereas non-stationary presents a variable variance (Wu, Iyer, and Wang 2018). Thus, non-stationary environments should be the only cause of unexpected uncertainty, and stationary environments should only have expected uncertainty. However, while being subject only to expected uncertainty, humans typically behave as the environment were non-stationary, thus producing unexpected uncertainties (Ryali, Reddy, and Yu 2016). While the functional reasons behind these behaviors are not clear, it has been proposed that this emerge because sustaining the belief that environments are non-stationary does not prove to be problematic in stationary ones (Ryali, Reddy, and Yu 2016) or because stochasticity in decisions may provide a sufficient heuristic in many natural environments (Reverdy, Srivastava, and Leonard 2014).

Under non-stationary environments, contingencies change, so animals are faced with the dilemma of either exploiting or exploring (Sutton and Barto 2018). Exploiting means that behavior should be consistent with previously learned reward contingencies. On the other hand, exploring tries to re-sample the environment to improve or re-learn current contingencies. The exploitation-exploration balance has been linked to the expected and unexpected uncertainty (Cohen, McClure, and Yu 2007), as unexpected uncertainty should increase exploratory behavior to boost learning of new contingencies, whereas if only expected uncertainty is

present, behavior should exploit current knowledge. However, exploration could be triggered by ‘boredom’ when environment properties are extensively learned (Aston-Jones and Cohen 2005).

Here we briefly exposed the different environmental properties of food-seeking behavior to generate good strategies and maximize gain. We proposed that natural environments are inherently stochastic, and animals adapted to sense various aspects of uncertainty regarding their actions within the environment. However, such pivotal importance of uncertainty in food-seeking behavior could be contested when considering perceptual abilities as the primary means of informing foraging.

Perceptual abilities are always limited in some regard, and such limitation can be regarded as the perceptual range of a given animal (Fletcher et al. 2013). If an animal must know what is beyond such perceptual range, displacement is needed. However, to inform such displacement memory, perceptual information integration or other strategies should come into play. In many classical models, animals can somehow integrate information about resource quality and distribution into an environment mean (Charnov 1976). However, perceptual omniscience is not the case, and integration of environmental information is dependent on times, so including non-local information (outside perceptual range) such as resource gradients prove helpful for the foraging animal (Fagan et al. 2017).

Even when local and non-local information can improve foraging success, there is still an issue on how perceptual information behaves regarding movement and spatial distance. The speed-perception tradeoff describes how perceptual abilities are degraded as speed is increased (Campos, Bartumeus, and Méndez 2013), and as rapid approaching speeds are required to capture prey or obtain food resources while relying on local perceptual information (Fagan et al. 2017) this tradeoff presents an issue to food-seeking behavior. Moreover, the intensive-extensive tradeoff points how finding food-resource nearby impairs finding resources far-away (Raposo et al. 2011; Bartumeus et al. 2016). Both tradeoffs imply that in order to properly obtain knowledge about the environment and actually achieve success in obtaining food leads to perceptual uncertainty and requires a fine balance between exploration and exploitation.

In order to deal with such tradeoffs, animals establish two distinct behavioral modes: (a) local search and (b) relocation. Local search is predominantly informed by perceptual information, while the relocation behavior shows signs of a stochastic process with Lévy-like distributions (Bazazi et al. 2012). While there has been discussion of Brownian-like random movements guiding local search, this is most likely an emergent property caused by frequent food encounters (de Jager et al. 2014), so this shifts from a random relocation process to a perceptually guided local search, are in part result of an increased frequency of food encounters. Thus, the overall food-seeking strategy derives from a combination of random and perceptually informed movements (Balogh et al. 2020).

Given the limitation in perceptual abilities, uncertainty seems to be inescapable. Even when an experienced animal can integrate optimal foraging paths in non-stationary environments, random searches with distinct cycles of exploration/exploitation phases persist (Kembro et al. 2019). Furthermore, introducing stochasticity in food-seeking behavior improves success as it makes strategies more resilient to cognitive errors derived from perception (Campos et al. 2020). The persistence of strategies that permits the balance between exploitation, exploration, and relocation (Campos, Bartumeus, and Méndez 2013), even when they are not technically needed (Ryali, Reddy, and Yu 2016) shows how relevant is uncertainty in the development of food-seeking behavior. In this section, we presented how stochastic properties of the environment lead to behavioral adaptations to deal with the resultant uncertainty by favoring strategies that favor the reduction of uncertainty (Peters, McEwen, and Friston 2017). In the next section, we will examine models that consider the case of foraging in uncertain environments, which informs about the underlying processes in food-seeking behavior.

Foraging models and underlying processes in food-seeking behavior

One of the way classical models such as (Charnov 1976) dealt with modeling foraging in uncertain environments was with the assumption of perfect knowledge. Animals should stay seeking food within a patch for as long the capture rate is above the capture rate of the environment (Charnov 1976), which implicitly assumes that somehow the animal is able to compute such capture rate. While such assumptions may sound unrealistic, there is some support for this as an experienced forager may learn and integrate information about the environment to closely approximate the perfect knowledge (Marshall et al. 2016).

On the other hand, and in consequence of the previously exposed relation between foraging and uncertainty, a model presented here should account for such relation. First, the rules determining the results of the interaction between animal and environment are assumed to be unknown or only partially known due to the stochastic nature of the environment. Then, the animal may take any action a within a set of possible actions $a \in A$ for a particular state of the environment s . Any action a causes an stochastic transition from a state s to another state s' . As such, the result of an interaction between animal and environment can be described by its value q , which is a function of both action and current environment state $q(s, a)$. Such model of action, state, and value corresponds to a Markov decision process (Sutton and Barto 2018). In this model, all environment dynamics are described by the probabilities $p(s', r|s, a)$, where r is the obtained reward (interaction outcome), and such probabilities are defined for every pair of a and s . We could consider a Markov decision process to include the perceptual noise which we deemed inherent to food-seeking behavior by considering that states s is paired with an observation o made by the animal to infer state s , because the state cannot be directly observed or there is some

sensory noise. As such, animals consider environment states as the conditional probability of any particular observation given a state $p(o|s)$, giving a belief of the current state based on perceptual information (Ma and Jazayeri 2014).

To model how an animal represents the value of a given option $q(s, a)$ in a non-stationary environment, this value is a distribution over possible values that is updated every time an action a is executed. For the simple case where rewards are obtained or not $q(s, a)$ has a Bernoulli distribution $p(X = \text{reward}) = a$ and $(p(X = \text{noreward}) = 1 - a)$. Then, these probabilities can be modeled with the Beta distribution, which takes parameters α and β . With $\alpha = 1, \beta = 1$ the Beta distribution produces a uniform distribution over $[0, 1]$ successfully representing the uninformed prior probability for the rewards. To generate the posterior probability every time the reward process results in a reward, the parameter α increases by 1. On the other hand, if no reward is obtained, the parameter β increases by 1. Finally, the mean is defined as

$$\frac{\alpha}{\alpha + \beta}$$

and its variance by

$$\frac{\alpha\beta}{(\alpha + \beta)^2(\alpha + \beta + 1)}$$

With these simple statistical properties of the Beta distribution, we can represent uncertainty over the expected rewards for any given a and s . If the exploration is defined by the posterior, then it can be considered a Thompson sampling strategy (Thompson 1933). To select an action a a posterior is built for every action and updated according to the previously stated rules, then for each posterior, a reward estimate \hat{r} is sampled greedily so the action selected is $a = \operatorname{argmax}_{a \in A} \hat{r}(a)$ where A is the set of possible actions within an environment (Wang and Zhou 2020). This processes must be performed for every state, limiting tractability by the the number of states. In general terms, a solution for this is to consider the reward vector as a weighted average over past rewards, with a step-size parameter $((0, 1])$, the lower the value of this parameter more weight is given to recent rewards, on the other hand, if its closer to 1, then all the reward history is equally considered. More complex consideration of this problem include modeling non-stationarity as Poisson arrival process that modifies the means rewards (Ghatak 2020), bayesian approaches to modulate past observed rewards (Raj and Kalyani 2017), and explicitly modeling environment volatility in a bayesian setup (Behrens et al. 2007).

While this general model can work in non-stationary environments, it doesn't consider explicitly the belief of the current state based on the perceptual information received $p(o|s)$. For this addition, a probability for every $o \in O$ by state is necessary, where O is the set of all particular observations o . To model state beliefs, the goal is to obtain the function that finally maps observations

o to action a given an underlying model that relates states with observations, a hidden Markov model (HMM) represents this. HMM generates conditional probability distributions $p(o|s)$ and bayesian, among other methods for obtaining such model given only actions and observation has been proposed (Funamizu et al. 2012; Yoon, Lee, and Hovakimyan 2018; Piray and Daw 2020).

In this section, we offered the elementary considerations for a model of food-seeking behavior in non-stationary environments with uncertainty over action outcomes due to perceptual limitations or noise. Thompson sampling was considered as the base for this due to its simplicity and elegance in modeling exploration/exploitation by computing uncertainty. The goal of these consideration was not to establish or to specify a complete model but to provide a framework relating uncertainty with the exploration/exploitation dilemma and perceptual limitations shown theoretically and empirically in the previous section.

Computing uncertainty

Uncertainty arises from having more than one option, and that the motivation to opt for one of those options is somewhat distributed, and there is no one option that is always preferred. Considering that the probability of choosing any given option has a uniform distribution, then uncertainty increases proportionally with the number of options. Shannon entropy (Shannon 1948) formalizes this intuition

$$H = - \sum_{i=1}^n p_i \log_2 p_i$$

So maximum entropy (one bit) is achieved when all the alternatives have the same probability, such as a coin flip. However, if the coin happens to have two heads, then Shannon entropy is 0.

If we consider a simple environment with only one state s , one action a initiate a food-seeking bout, and only two possible outcomes food is found (p) or not found ($q = 1 - p$), then $H = -(p \log_2 p + q \log_2 q)$. If an animal performs multiple food-seeking bouts and non of them are successful $H = 0$ the same is true if all are successful. However, if the probability of a successful food-seeking bout is 0.5, then entropy is maximized $H = 1$. Neural representation of entropy has been found in the middle cingulate cortex (MCC) for the particular implementation of encoding outcome entropy (Goñi et al. 2011; Gloy, Herrmann, and Fehr 2020) so this computation seems to be biologically plausible. However, entropy is not available as sensory input must derive from actions and outcomes, which are dependent on the environment state. Previously, through Thompson sampling, we provided a way in that entropy could be encoded as variance in the posterior distribution. Nevertheless, a more direct way to compute entropy is possible through the prediction error.

The classical model of Rescorla-Wagner (Rescorla et al. 1972) modeled how

animals could predict the reinforcing value of a given stimuli

$$y_t = y_{t-1} + \alpha \delta_n$$

where the value representation of the stimuli y is obtained by considering the previously estimated value y_{t-1} , but weighted by a learning rate α and a prediction error δ . δ is the simple difference between the expected reward and the actual reward $\delta_n = r_t - y_t$ where r_t is the obtained reward, an extension to this has proposed by (Sutton and Barto 2018) where the prediction error consider an estimate of the rewards that give more weight to current rewards while still considering past rewards

$$\delta_n = R_t + \gamma \hat{V}_{n+1} - \hat{V}_n$$

γ is a discount factor $0 \leq \gamma < 1$ for all the history of rewards, and \hat{V} is a proxy for the true value of the reward. Finally, $\alpha : [0, 1]$ is the learning rate which effectively weights the reward prediction error δ so to make small updates $\alpha \approx 0$ or rather large ones $\alpha \approx 1$.

The simple model presented allows deriving a prediction error based on experience and the learning rate can be set lower to simulate unexpected uncertainty or higher to simulate expected uncertainty. However, α in such model is a hyperparameter, thus not derived from experience. Pearce and Hall (1980) model proposes that α can be controlled by the prediction error magnitude $|\delta|$ so

$$\alpha = \gamma |\delta_{n-q}| + (1 - \gamma) \alpha_{n-1}$$

Higher entropy on reward outcomes increases the minimal error probability (Feder and Merhav 1994), thus increasing $|\delta|$, and consequently α . The behavioral result is that the animal should increase learning for options with the uncertain outcome by directing its attention (Diederen and Fletcher 2021).

Dopamine (DA) encodes prediction error (Nasser et al. 2017; C. D. Fiorillo 2003; C. D. Fiorillo 2011; Lak, Stauffer, and Schultz 2014; Glimcher 2011; Khaw, Glimcher, and Louie 2017; Gershman and Uchida 2019), more specifically, DA phasic median activity encodes reward probability as positive linear relationship for the conditioned stimulus, and as a negative linear relationship for the unconditioned stimulus (C. D. Fiorillo 2003). Effectively encoding the prediction of the unconditioned stimulus, and the surprise for the unconditioned stimulus, if a reward has a low probability obtaining it should be ‘surprising.’ Moreover, the change in sustained activation encodes rewards probability analogous to entropy, that is, displaying a peak of activity at probability 0.5 [C. D. Fiorillo (2003) Moreover, the change in sustained activation encodes rewards probability analogous to entropy, that is, displaying a peak of activity at a probability of 0.5 (C. D. Fiorillo 2003). Hippocampal activity has been shown to reflect Shannon entropy and adaptation predicted by prediction error minimization (Schiffer et al. 2012), similar activity is also present on the striatum (den Ouden et al. 2010), substantia nigra (Zaghloul et al. 2009), and ventral tegmental area (Iordanova

et al. 2021). Moreover, DA activity fits the classical reinforcement models as ventral tegmental DA support cue-reward learning, the modifications of previous cue-reward associations (Steinberg et al. 2013; Chakroun et al. 2020), and capable of dealing with exploration/exploitation via tonic and phasic signaling, respectively (Beeler et al. 2010).

There is substantial evidence that DA neurons, specifically in the VTA, serve the functional role of computing reward prediction errors (Watabe-Uchida, Eshel, and Uchida 2017), by weighing inputs from multiple brain areas, most remarkably the lateral hypothalamus, dorsal and ventral the striatum, ventral pallidum, and subthalamic nucleus (Tian et al. 2016). However, acetylcholine (ACh) and norepinephrine (NA) associated with expected and unexpected uncertainty, respectively (Yu and Dayan 2005), which are mainly produced in the basal forebrain (Sturgill et al. 2020) and locus coeruleus (LC) (Sales et al. 2019; Aston-Jones and Cohen 2005). ACh antagonism has been shown to increase the response sensitivity to expected uncertainty within a task (Marshall et al. 2016), providing evidence that ACh represents expected uncertainty. On the other hand, NA for new contingencies. On the other hand, LC tonic activity represents unexpected uncertainty (Payzan-LeNestour et al. 2013; Aston-Jones and Cohen 2005).

In this section, we presented simple computational models that consider uncertainty by using the information provided by the reward prediction error, which is an extremely simple computation that is likely to be implemented by DA activity in the VTA, with additional modulation by ACh and NA possibly controlling the sensitivity of DA to expected and unexpected uncertainty. In the following two sections, we will show empirical evidence on how food-access uncertainty increases food-seeking behavior, and propose orexin as a potential mediator of uncertainty-driven foraging.

An adaptive strategy in modern times

Natural environments are limited in food resources, and food-seeking behavior results from an adaptation to such environments. If the characteristic property is scarcity, then animals should approach cues with the highest associative strength to actual food resources, this approach (Montague, Dayan, and Sejnowski 1996) suggests that prediction error signal if the current state is better or worse than expected, so animals should prefer options with the highest expected value (Kacelnik and Bateson 1996). However, uncertainty in food delivery increases lever pressing and reduces the time latency to approach lever (Anselme, Robinson, and Berridge 2013). Creating intermittent access to high-fat diets generates binge-eating behavior (Hess et al. 2019; King et al. 2016; Lardeux, Kim, and Nicola 2013), increases reinforcement value upon withdrawal (McGee et al. 2010) and operant behavior without withdrawal (Wojnicki, Babbs, and Corwin 2013; Wojnicki, Stine, and Corwin 2007; Wojnicki et al. 2015), psychomotor behavior (Hardaway et al. 2016), DA and Ach release (Rada, Avena, and Hoebel 2005). Mainly because of logistic reasons intermittent access is provided at the same

time of days (in most cases), and that allows animals to accurately predict the arrival of food, although with some inconsistencies within animals (Luby et al. 2012). However, the behavioral effects, except anticipatory behavior, are common if intermittent access is completely random or given at certain times of the day (Muñoz-Escobar, Guerrero-Vargas, and Escobar 2019).

Intermittent feeding schedules, and in general uncertainty of food-access disrupts eating patterns. Food-seeking behavior is increased to avoid starvation when a food shortage is predicted, and as previously noted, this derives in increasing exploration, amount of foraging bouts, and time expended in foraging (Harris, Chapman, and Monfort 2010). This could be translated to the concept of food insecurity, which defines the perception of how secure food access is (Dhurandhar 2016), which is positively correlated with positive energy balance (Dhurandhar 2016), increasing preference for high-fat alternative (Nettle, Andrews, and Bateson 2017), which corresponds to the food of cheap access in developed countries where this effect is more pronounced (Moradi et al. 2019) in females (Dinour, Bergen, and Yeh 2007; Nettle and Bateson 2019). The strategy responsible for overweight in food-insecure individuals are to overeat fats and carbohydrates in periods of high food availability (Stinson et al. 2018).

In modern urban environments, high-fat food is of easy access, coupled with a food-seeking behavior which seeks to maximize energetic gain, when food shortage is predicted due to food-access uncertainty, can create overweight in the population because the mechanism is adapted to low resource environments, however, in developed countries, caloric density is extremely high, so increasing food-seeking behavior results in excessive caloric intake. In the following section, we present orexin as a potential mediator of uncertainty-driven foraging because of its pivotal role in both reactive and predictive homeostatic control (Burdakov 2020), and motivated behavior (Tyree, Borniger, and de Lecea 2018).

Orexin as a potential mediator of uncertainty-driven foraging

Animals respond to the environment by seeking to preserve certain physiological parameters within a normal range, this homeostatic process is highly adaptive and can generate transient changes (Davies 2016). The hypothalamus comes as a relevant structure in the homeostatic process by being capable of controlling arousal levels (Adamantidis, Carter, and De Lecea 2010; Kossse and Burdakov 2014), motivation for food intake (Castro and Berridge 2017), receiving internal status information of fat deposits via leptin signaling (Pandit, Beerens, and Adan 2017; Meister 2000), and gastrointestinal status via ghrelin (Müller et al. 2015; Toshinai et al. 2003). Together, this functionality takes the hypothalamus to a pivotal role in the homeostasis process, specifically relating to controlling food intake.

Orexin or hypocretin is a neuropeptide with few neurons producing it most of them located within the lateral hypothalamus and perifornical area, but with large projections throughout the brain (Chowdhury et al. 2019). Its

functions range from regulating sleep/wakefulness states (Chemelli et al. 1999) and energetic balance (Yamanaka et al. 2003). Thus lateral hypothalamus orexin neurons are in a well-suited spot to control foraging-related behaviors. Orexin activity promotes locomotor activity but is rapidly inhibited upon contact with food (González et al. 2016), activity increases upon sucrose predictive cues (Hassani et al. 2016), and in certain subpopulation, the increased spontaneous physical activity is directed towards food sources (Zink et al. 2018). Thus, orexin-related activity can be interpreted as food procuring (Zink et al. 2018), further support for this interpretation come from orexin increasing olfactory activity (Prud’homme et al. 2009), enhancing visual attention (Zajo, Fadel, and Burk 2016), impairment of spatial working memory in orexin knockout mice (Dang et al. 2018), among others that have been classified as foraging-related behavior by Barson (2020).

Orexin role in food-seeking behavior is not sufficient to suggest its role in uncertainty-driven food-seeking behavior, however its connectivity to VTA, LC and basal forebrain (Siegel 2004), which corresponds to inputs into DA, Ach and NE activity, respectively, might hint at orexin role in promoting food-seeking behavior for prediction-error derived uncertainty, expected and unexpected uncertainty. VTA projects glutamatergic inputs into the nucleus accumbens shell, specifically into parvalbumin GABAergic interneurons, activation of such neurons results in inhibited medium spiny neurons activity into the lateral hypothalamus (Qi et al. 2016), these connections are known to be inhibitory (O’Connor et al. 2015; Connor_Etal_2015; Perez-Leighton et al. 2017), and input inhibition increases lateral hypothalamus activity (Stratford and Kelley 1999; Gutierrez et al. 2011). Furthermore, as we mentioned in previous sections DA activity in VTA is related to environmental uncertainty, which could increase lateral hypothalamus activity through dopaminergic inputs to the supramammillary nucleus (Plaisier, Hume, and Menzies 2020), and indirect action by orexin derived increased firing in VTA that further inhibit nucleus accumbens shell. This could result in a net increase in food-seeking behavior via uncertainty augmented activity in the VTA.

Orexin signal depolarizes LC increasing its firing (Hagan et al. 1999), which can promote task disengagement (Kane et al. 2017), alter network representation of tasks (Grella et al. 2019), and update world models (Sales et al. 2019), likely via promotion of exploratory behavior related to tonic firing (Aston-Jones and Cohen 2005). These data support the integration of orexin with unexpected uncertainty and exploration. Orexin also, synapse on cholinergic neurons in the basal forebrain, promoting acetylcholine release, which also creates excitatory influence on orexin neurons, generating a positive feedback circuit (Sakurai et al. 2005). Cholinergic basal forebrain activity encodes valence-free prediction error (Sturgill et al. 2020), so DA and Ach could generate similar uncertainty-drive excitation of orexin neurons. However, Ach activity might be related to reducing the effects of prediction error in learning by signaling a smaller variance (Puigbò et al. 2020; Yu and Dayan 2005) similar to expected uncertainty signaling.

In this section, we provided a plausible circuit where orexin activity acts as a hub relating, prediction error, unexpected uncertainty, and expected uncertainty. This puts orexin as a candidate neuropeptide for dealing with uncertainty-driven food-seeking behavior as it can both integrate environmental and internal status information, and promote locomotor activity to procure food. We derived this function taking theoretical and empirical finding from foraging theory, computational models of reinforcement learning and literature on homeostatic control of food intake, allowing us to propose a functional role for orexin situated in the proper evolutionary and environmental context.

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