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Competitive Re-weighting of Food and Social Reward Prediction Error by Deprivation States

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Abstract. Food and social interaction are important rewards, but whether hunger and social isolation independently or competitively affect reward prediction errors (RPEs) for these rewards remains unclear. In this proposal, adult dopamine transporter–Cre mice will first be tested in a 2 × 2 within-subjects design comparing the control, food-deprived, socially isolated, and doubly deprived states. Tests measuring food-seeking, social preference, and choice between food and social stimuli will assess whether each deprivation selectively alters the value of the corresponding reward. Second, fiber photometry will record ventral tegmental area (VTA) dopamine neuron activity during trials with expected, unexpected, and omitted food and social outcomes, distinguishing reward responses from positive and negative RPEs. Third, mice will choose between food and social options of approximately equal value, with occasional changes made to reward identity, magnitude, or delivery. Behavioral and neural data will be compared with predictions from selective gain, competitive reweighting, and dominant need models. Finally, follow-up experiments will examine whether observed reweighting reflects intrinsic VTA changes, hormonal modulation, or altered upstream input. This proposal predicts that deprivation states will selectively enhance corresponding RPEs. Combined deprivation will assess whether these signals remain separate, compete in their expression, or merge into a single dominant motivational signal.

Keywords: reward prediction error, ventral tegmental area, social reward, dopamine neurons, social isolation

1. Introduction

Brains often have to decide between two outcomes that are biologically required for survival, as choosing one will delay accessing the other. Studying this kind of competition is convenient with food and social stimuli as they both involve the mesolimbic dopamine pathways. Overlapping groups of dopamine (DA) neurons in the ventral tegmental area (VTA) are triggered by both food and social stimuli, with the fraction of neurons responding to both types of stimuluses increasing during deprivation of these stimuli [1]. Social interaction can also produce reward prediction error (RPE); when undergoing associative learning, VTA dopamine neuron activity shifts from the reward to a prediction, which produces a decrease in expectation when the expected social interaction is not obtained [2]. Though these conclusions tell us that there is common neural wiring, there are still

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unanswered questions on whether food and social rewards are processed and evaluated under a single common neural signal or separate stimuli specific signals.

Social need is similar to homeostatic drive when it comes to deprivation; for example, 10 hours of social isolation for human beings led to social cravings indicated by certain midbrain responses similar to the neural signals produced when humans desire food after fasting [3]. In adolescents, acute isolation was shown to be associated with higher reward responsiveness and reward learning [4]. In lab rats, a social-sucrose choice task showed that deprivation states affect the choice of reward as well as the neural representation of reward, with effects in the medial prefrontal cortex varying by sex [5]. The listed findings from various articles constitute an arrangement of previous findings that form a basis for comparing food and social reward, for taking into account sex as a variable, and for controlling locomotor activity in the experiment.

Further on reward valuation, studies have suggested that rewards from different types of stimuli merge into a common subjective scale of valuation, with dopamine combining information on risk, amount, and identity in line with an organism's behavioural preference [6]. But at the same time, social reward is dictated by specific pathways as well as its shared mesolimbic pathways [7], and separate groups of VTA neurons hold the capability to allow inhibition of drug-seeking by valuation of social reward [8]. In the matters of reward valuation in the brain, reward prediction error (RPE) is the difference between the expectation and result of reward, meaning a positive error is processed when an unexpected reward is received, miniscule error when rewards match expectations, and negative error when expected rewards are missing [9]. Even though VTA DA-neurons vary in uses [10], a similar RPE response could be observed in most neurons that showed differences only in the scale of signals [11]. This proposed project therefore intends to answer the question on how hunger and social isolation competitively affect food and social RPE.

2. Method

2.1. General experimental design

Adult (10–14-week-old) dopamine-transporter internal ribosome entry site Cre (DAT-IRES-Cre) mice of both genders will be used for this experiment, and will be subjected to four states of deprivation/satiety: fed/non-isolated, non-fed/non-isolated, fed/isolated, and non-fed/isolated the exact states of deprivation for food/social will be 15-20 hours of fasting [1] and 24 hours of isolation [12]. Water will remain accessible in all states. A minimum of 72 hours of regular social interaction and feeding will separate blocks of imposing deprivation states. Habituation (at least one week), matching of unfamiliar same-sex mice, balanced assignment of experimentation, and blinded scoring will be used to reduce confounds. The final sample size will be determined by a pilot informed power analysis for the experiment. VTA DA-neurons will be monitored by a CRE-dependent genetically encoded calcium-indicator (GCaMP) that is injected into the VTA and subsequent fiber photometry through a similarly implanted optical fibre [13]. Data from the calcium-dependent and isosbestic channels will be recorded through fibre photometry, and digital pulses responsible for synchronizing cues, pumps, doors, licking, and choices [13]. After experiments, tyrosine hydroxylase immunostaining will be used to confirm colocalisation of DA neurons, spread of the virus, and that the fibre is appropriately positioned. Cases of absent expression, insufficient overlap, or fibres lying outside the VTA will be excluded based on preregistered exclusions.

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2.2. Experiment 1: verification of reward value

This experiment seeks to verify that hunger and deprivation states selectively alter the value of food and social rewards. The experiment will assess mice food valuation by the measurements of approach latency, consumption latency, time spent entering the reward zone, the amount consumed, licking, and operant responses. Similarly, assessing social valuation, through a three-chamber or single-target assay, will use measurements of approach latency, sniffing, interaction time, and the social preference index: calculated by (time spent near social target - time spent near the empty enclosure) divided by (total time). Locomotor or anxiety-related compounds will be detected and measured using distance, speed, and the use of an open-field control.

A preliminary choice assay will use food in the form of 10 microliters of 10% sucrose, valued against around 8 seconds of social interaction with a same sex mouse that is unfamiliar, an established two-choice experimental procedure [5]. Distance, delay, level of effort, length of access, and reward size will vary until control choices reach near 40-60%.

2.3. Experiment 2: direct measurement of food and social RPEs

This experiment seeks to distinguish if dopamine activity observed is genuine reward-prediction error instead of a non-specific response to movement or receiving reward. Food related aspects and social expectations will be trained separately by different cues. In each trial there will be a baseline phase, suggested 2-second cue, fixed delay between cue and outcome (delivery or denial), delivery of the reward, and randomly generated interval between trials that is 30 to 60 seconds. Training goes on until increases in anticipation and dopamine activity changes from association with the outcome to association with the cue.

Through the duration of learning, trials will be mixed to include expected reward, unexpected reward, and omission of reward with 80%, 10% and 10% frequency respectively. In expected trials, cued rewards are given; in unexpected trials, rewards are given without cue; and in omission trials, the cued reward is not provided. Pump-only, empty-gate, and matched-sound control conditions will separate the desired reward from the apparatus. Within each of the previously mentioned four states, the mouse will experience both food and social reward separately. If RPE is genuine, there should predictably be a positive spike in unexpected trials, smaller neural response in expected trials, and a negative response in omission trials [2].

For the results and their significance, if food-related signals selectively increase when the mouse is under hunger, and social-related signals selectively increase when the mouse is isolated, this would indicate RPE gain is directly linked to its corresponding deprivation state. By contrast, if neural response to the reward of the non-deprived state is suppressed when the mouse is under the other deprivation state, this would suggest competitive weighting of food and social valuation. Lastly, if changes are seen only in expected trials, it is suggested that deprivation states will only change expected value of rewards instead of full RPE in all cases.

2.4. Experiment 3: direct competition between food and social rewards

This experiment expands on experiment 2 by measuring results upon direct competition between food and social reward, whereas previously they were measured separately. Two illuminated nose-poke ports will be used to indicate food and social reward to the mice, and one will dim when the mice choose the other. Firstly, the mice will be separately trained on each option, with left-right

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assignments counterbalanced. In training, VTA activity, choice made, reaction time, trajectory, collection of reward, and any decreases in hunger or social need during training will be logged.

For a minority of the trials, rewards will be omitted, changed in magnitude, or food and social rewards will be swapped. This is done to ensure that VTA DA-neurons can predict identity and value of the outcome [14]. Comparison of the previously established possible results and their linked suggested models (in experiment 2) will then be compared through held-out prediction, information criteria, and parameter recovery.

2.5. Experiment 4: mechanisms of state-dependent reweighting

This experiment seeks to determine the how of any state-dependent reweighting. The experiment will be split into experiment 4A, 4B, and 4C.

Experiment 4A will use single-nucleus RNA sequencing or targeted assays on VTA DA-neurons along with whole-cell measurements of membrane potential, input resistance, firing threshold, spontaneous firing, and synaptic currents. Transcriptomic effects will continue to be correlational unless they are found to be simultaneous with changes of in vivo RPE gain and excitability.

Experiment 4B will analyze ghrelin, leptin, insulin, oxytocin, and other signals from the stress axis [15]. Social reward is dependent on oxytocin-serotonin signaling in the nucleus accumbens; oxytocin controls the reward-specific DA neurons in the VTA [16], and hypothalamic oxytocin has an effect on VTA plasticity caused by isolation [17]. A candidate must vary with the state, show the phenotype when it is activated, and have the phenotype weakened when it is blocked.

Experiment 4C will use retrograde tracing, photometry restricted to projection areas, and phase specific perturbations to identify the inputs to the VTA which encode cues, choices, outcomes, or omissions. When selecting mice the amygdala-hypothalamus social circuitry [18], the way dopamine errors are retuned by social feedback [19], and the convergent hypothalamic-mesolimbic reward pathways [20] will be taken into account. Controls using viruses, light only, and no ligand will be used to check for non-specific effects.

3. Planned analysis, rigour, and animal welfare

Analysis will be done by correcting photometry traces to make them isosbestic, normalized, and formatted as z-scores relative to a pre-established baseline. Predefined outcomes are peak amplitude, area under the curve, time taken to reach peak amplitude, and minimum omission response. A mixed effects model will be used to examine interactions between deprivation states and types of rewards and trials, with random intercepts for each mouse included and also using covariates like sex, movement, and session half. Generalised mixed models will be applied for binary choices. Multiple comparisons will be adjusted for and effect sizes will be given along with confidence intervals.

After pilot optimization, windows, exclusions, outcomes, and models will be preregistered. Additionally, procedures will require approval from the animal-care committee and will need to comply with welfare requirements. Repeated measures will reduce the number of animals needed, with only separate cohorts being used for the terminal assays.

4. Conclusion

The goal of this proposed project is to uncover the distinction between RPE and ordinary neural reward responses. The proposal involves behavioural validation, recording in the VTA, direct choice between the rewards, and computational comparison and mechanistic follow-up. Additionally, trials

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involving the triad of expected, unexpected, and omission trials distinguish RPE from standard reward response, while locomotor controls protect interpretation of reward value.

Selective gain suggests separable signals in the brain's neural pathways, reciprocal enhancement and suppression would suggest competitive reweighing, and a single need being prioritized would suggest a dominant-RPE mechanism. Tests using identity substitutions will determine whether the unified activity still maintains reward identity when both nutritional and social needs are not settled.

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