A line attractor maintains aggressiveness during feeding in "hangry" mice

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Running Title: Effect of food deprivation on hypothalamic line attractor dynamics

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SUMMARY

Aggression evolved to protect resources such as food from competitors, but animals must balance fighting and feeding so that they facilitate rather than hinder re-establishment of energy homeostasis. How this balancing is computed is not well understood. We have approached this problem at the level of neural population-coding by examining the effect of progressive starvation on a hypothalamic line attractor that encodes an internal state of aggressiveness. Moderate fasting yielded "hangry" mice, decreasing attack latency and increasing attack frequency. In parallel, line attractor ramping rate and stability were increased, suggesting that hunger enhances aggressiveness by modifying neural dynamics. In contrast, prolonged starvation inhibited aggression and eliminated the line attractor. In satiated mice, titrated acute chemogenetic activation of arcuate AgRP neurons recapitulated the biphasic effects of progressive starvation, suggesting that a continuous increase in hunger exerts bi-directional influences at different intensities. When confronted with food and an intruder, hangry mice alternated between feeding and fighting. During eating, population neural activity moved out of the line attractor while activity in the attractor dimension remained unchanged. Following feeding, activity rapidly relaxed back into the attractor and aggression resumed. Thus, the line attractor may serve to keep hungry animals primed for aggression during intermittent feeding bouts.

Keywords | Dynamical systems analysis, interacting internal states, hunger, aggression, emotion, homeostasis, flexible innate behaviors, state-dependent modulation

INTRODUCTION

Aggression evolved to protect resources essential for individual survival and reproduction such as food, territory, mating partners, or offspring[1]. However, fighting is mutually exclusive with behaviors that mediate resource acquisition and consumption. Thus, for example, hungry animals must dynamically adjust their choice between feeding and fending off competitors for food so that fighting facilitates, but does not ultimately interfere with, re-establishment of energy homeostasis[2-5]. This choice likely depends upon multiple factors such as residual energy reserves, quantity and quality of food resources and perceived aggressiveness of the competitor. How this dynamic decision-making is computed by the brain to optimize flexible behavioral prioritization[6] is not well understood.

As a first step towards addressing this question, we have investigated how aggressive behavior and brain activity are modulated by the duration of starvation. Hunger is well-known to enhance aggressiveness in multiple species[7-10], and is experienced in humans as "hanger"[11-13]. Surprisingly, this phenomenon has not been convincingly demonstrated in mice. To the contrary, recent data suggest that food deprivation inhibits rather than enhances aggression in mice[5,14]. Older studies have described bi-directional effects of fasting duration on aggression[15], but characterization of these effects was limited.

Aggression is controlled by estrogen receptor-1 (Esr1)[16]- and progesterone receptor (PR)[17,18]- expressing neurons located in the ventrolateral subdivision of the ventromedial hypothalamic nucleus (VMHvl[19]; reviewed in refs[20-22]). VMH is also a well-known neural hub for controlling feeding and metabolic regulation[23-25]. Whether and how hunger controls aggression via influences on VMHvl[Esr1/PR] neurons is not clear. A suppressive effect of starvation on aggression was shown to be mediated by VMHvl-projecting BNST neurons that receive inhibitory input from NPY-responsive medial amygdala (MeA) neurons[14], but the role of VMHvl[Esr1/PR] neurons was not investigated.

Given the complexity of VMHvl cell types[26-29], circuitry[25,30-32] and single-unit activity[19,33,34], we have asked whether aggressiveness is modulated by food deprivation at the level of population coding and manifolds in neural state-space[35-39]. Attractors are a

well-established population coding mechanism for computing cognitive variables[39-44].
Recently, we identified an approximate line attractor[45] that encodes a scalable and
persistent internal state of aggressiveness in VMHvl[46-48]. Other data suggest that attractor
dynamics may encode physiological internal states as well[49]. For example, competition
between feeding and drinking is reflected in dynamical interactions between apparent
basins of attraction for hunger vs. thirst[50,51].

Here we report that different durations of starvation exert strongly correlated bi-
phasic influences on aggressiveness and on VMHvl[Esr1] line attractor dynamics, an effect
recapitulated by titrated short-term chemogenetic activation of arcuate AgRP-expressing
"hunger"-promoting neurons[52-54] in satiated mice. Furthermore, activity in this line
attractor remains persistently elevated when "hangry" mice alternate between feeding and
attack bouts in a behavioral choice paradigm. These results suggest that modifications of
VMHvl line attractor dynamics may underlie the neural coding of "hanger," and that this
attractor may play an adaptive role to keep hungry animals "primed" for attack while
replenishing their energy reserves.

RESULTS

Metabolic states modulate male aggression in a biphasic manner, establishing
hunger-enhanced aggression in mice

To determine the features of aggressive behaviors in male mice that are modulated
by metabolic states, we employed the standard resident-intruder (RI) assay[33,55] and
perturbed the resident's energy states by limiting food availability with different durations
of food deprivation before introducing a rival (*ad libitum*-fed) intruder (Fig. 1a). The same
resident mice under *ad libitum* feeding conditions served as within-subject controls, using
a cross-over design (Fig. 1b). The RI assay itself was performed in the resident's home
cage in the absence of food.

Mice that were food-deprived for 18 hours exhibited heightened aggression
compared to those fed *ad libitum*, as evidenced by a significant increase in time spent
attacking[6], the number of attack bouts, and a reduction in inter-attack bout interval

duration (although there was no change in average attack-bout duration; Fig. 1c-f). In
addition, the probability of attack following the initial aggressive encounter increased
under starvation (Fig. 1g). Notably, 18h-fasted mice showed a significantly shorter latency
to initiate the first attack than the same mice under *ad libitum*-fed conditions (Fig. 1h, i).

We also investigated whether there were additional changes in the kinematics[56] of
aggressive behavior under starvation. We employed machine learning (ML) to quantify
the intensity of aggression based on the values of different pose estimation[57]-derived
features, using seven key points assigned to each mouse (Fig. 1j; see Methods). Among
these features, we found that pixel change, a measure of movement velocity across
frame[57] (Fig. 1j, right-black), was significantly higher during aggression performed by 18-
hr-fasted mice compared to *ad libitum*-fed controls (Fig.1k, bar graph). This increase was
observed specifically during video frames annotated as attack bouts, but not during
sniffing bouts (Fig. 1k vs. 1l). This result corroborates our subjective impression that
aggression in mice fasted for 18 hours was more vigorous compared to that in fed animals.

We next sought to reconcile this observation with prior studies demonstrating that
food deprivation suppressed aggression in male mice[6,14]. This apparent discrepancy
could reflect methodological differences or dynamic biological interactions between
hunger and aggression states. To investigate whether the effect of hunger to promote
aggressiveness was a linear function of starvation time, we measured aggression after
shorter (~8 hr) or more extended (40 hr) periods of food deprivation. (The durations were
chosen based on body weight changes and compatibility with similar zenithal times for
performing behavioral assays; Extended Data Fig. 1a, Methods.) Mild starvation (8 hr)
did not significantly alter aggressive behavior compared to the fed states (Extended Data
Fig. 1b, c). In contrast, prolonged starvation (40 hr) dramatically attenuated aggressive
behavior, consistent with previous reports[14,15], and significantly increased attack latency
compared to *ad libitum*-fed mice (Extended Data Fig. 1d, e). Notably, the time spent
investigating male intruders was not significantly different across different energy states,
although there was a trend to increased sniffing after 40 hours of food deprivation
(Extended Data Fig. 1f; see also Fig. 3c and Extended Data Fig. 2a). Thus, food

deprivation had a biphasic effect on aggression in mice, with intermediate starvation
enhancing and prolonged starvation decreasing aggressive behavior[15].

We also observed a profound change in male sexual behavior during interactions
with female mice under intermediate fasting conditions[6] (Extended Data Fig. 1g). In the
absence of food, male mice exhibited a marked decrease in sexual behavior (such as
mounting and intromission toward female intruders) following 18 hours of fasting,
suggesting that a deviation from metabolic homeostasis can suppress sexual drive under
some conditions (Extended Data Fig. 1h-m). Remarkably, under these conditions, 20% of
males even displayed aggressive behavior toward female intruders, a behavior rarely
observed under *ad libitum*-fed conditions (Extended Data Fig. 1h-pie chart). This
observation underscores the potency of 18 hours of fasting to alter the balance of social
behaviors, increasing aggression while decreasing mating.

Intermediate starvation alters the ramping and stability of line attractor dynamics
representing the aggressive state

We next sought to characterize neural correlates underlying the hunger-induced
enhancement of aggressiveness; in other words, how is the internal state colloquially
termed 'hanger' encoded in the brain[46,47]? To this end, we measured the activity of
individual VMHvl[Esr1] neurons expressing GCaMP8m by performing *in vivo*
microendoscopic calcium imaging[58] in mice fed *ad libitum,* and in the same mice following
18 hours of food deprivation. This longitudinal imaging allowed us to track the same
population of neurons over several days (see Methods) to examine changes in their
relative activity across distinct energy states (Fig. 2a-d). We confirmed that mice with
GRIN lens implants and head-mounted miniature microscopes recapitulated the
phenotypic readouts of hunger-induced changes in aggressive behaviors (Extended Data
Fig. 2a-e).

First, we investigated whether 18hr-fasting caused changes in overall neural
activity or in the behavioral tuning of individual neurons. The mean, peak z-score activity,
and time to peak of z-score activity of all VMHvl[Esr1] neurons following the first sniff were
not statistically different between fasted and fed mice (Extended Data Fig. 2f-j). Choice

probability analysis of single-neuron behavioral tuning[33] confirmed that most neurons

(>70%) exhibited mixed selectivity for male-directed behaviors in both the fed and 18-hr

fasted states (Extended Data Fig. 2k, l, gray), consistent with prior findings in *ad libitum*-

fed mice[33,48,55]. Among behavior-tuned cells, the percentage of sniff- or attack-tuned

VMHvl[Esr1] neurons was not significantly different in fed versus fasted mice (Extended

Data Fig. 2k-m, q). Furthermore, the mean activity (post-sniff) of attack-tuned or sniff-

tuned populations was not affected by starvation (Extended Data Fig. 2n-p, r-t). Thus,

analysis of single-unit activity and behavioral tuning in VMHvl[Esr1] neurons failed to reveal

robust changes that correlated with the increased aggressiveness of 18 hr-starved mice.

We next investigated whether changes in the population coding of behavior could

be observed between fed and 18hr-fasted mice. As a first step, we used generalized

linear models (GLMs). Previous studies in females have indicated that GLMs using

behavioral regressors do not explain a high fraction of the variance in VMHvl[Esr1] neural

activity[59]; we confirmed the same was true for activity in both fed and fasted males

(Extended Data Fig. 3a, b). While inclusion of a cell-to-cell coupling term (which

incorporates correlations in activity among VMHvl[Esr1] neurons) in the GLM increased the

model fit[59-61], the mean variance in neural activity explained was still <50% in both

conditions (Extended Data Fig. 3c-f), a relatively poor fit.

Because the coupling term may reflect local connectivity, and since neural

dynamics can be influenced by local connectivity[62], we next examined whether neural

dynamics were altered by 18hr food deprivation. One measure of neural dynamics is

their decay time following peak activity. To assess this, we calculated the autocorrelation

half-width (ACHW)[33,63,64], a proxy for single-neuron persistence, for each neuron across

both conditions. This revealed a small but statistically significant increase in decay time

in 18hr fasted mice in the bulk VMHvl[Esr1] population (Extended Data Fig. 3g-j, mean

ACHW: 9.7± 0.3s for fed state vs 11.58 ± 0.3s for fasted state, p****<0.0001, n=6 mice).

As VMHvl[Esr1] neurons are heterogeneous[26], we investigated next whether there

were latent subpopulations of neurons in this population that might exhibit more robust

changes in dynamics than the population as a whole, following food deprivation. To do

this, we applied an unsupervised probabilistic modeling approach, recurrent Switching

Linear Dynamical Systems (rSLDS)[65,66]. This approach uses dimensionality reduction to

identify latent dimensions (factors) in VMHvl^{Esr1} population activity that differ in their

activity and dynamics. It then fits a linear dynamical system model to activity in this latent

dimension state-space, using machine learning (Extended Data Fig. 4a). Consistent with

prior studies[46,59], rSLDS models fit to data from both fed and 18 hr-fasted mice explained

a much larger fraction of the variance in neural activity (cvR^2 $\geq$90%; Fig. 2e) than was

explained by GLMs.

To interpret these models, we examined the "learned" dynamics matrix A of the

longest-lived state, fit by the model (Extended Data Fig. 4a). The eigenvalues of this

matrix yield the time constants of each of the latent dimensions[65,66]. Consistent with our

earlier studies[46-48,59], models fit to data from fed mice yielded one dimension (X_1) with a

substantially greater time constant than the next-slowest dimension (X_2), suggestive of a

"slow mode," or integration dimension (Fig. 2f-i, o; Extended Data Fig. 4g). This slow

mode is characterized by "ramping up" behavior during sniffing episodes, reaches its

peak level at the onset of attack, remains elevated between attack bouts and decays

slowly thereafter[46] (Fig. 2f-i, burgundy curves; Extended Data Fig. 4b). In contrast, the

orthogonal (X_2) dimension exhibited transient activity that peaked at the first sniff and then

declined rapidly (Fig. 2f-l, gray curves; Extended Data Fig. 4c). In 2D flow-field

visualizations of the state-space model, the X_1 dimension yielded a linear region of "slow

points" that may represent a leaky integrator or approximate line attractor[46,47] (Fig. 2r, s;

Extended Data Fig. 4h, dashed lines). rSLDS models fit to data from 18 hr fasted mice

yielded a qualitatively similar result, in terms of latent factors and their dynamics (Fig. 2g,

i).

To determine whether line attractor parameters differed quantitatively between fed

and 18 hr-fasted mice, we compared the ramping and decay phases of the projected X_1

integration dimension activity under the two conditions. Alignment of normalized z-scored

activity to the onset of the first attack revealed significantly steeper ramping dynamics in

fasted vs. fed mice (Fig. 2j$_i$). Importantly, comparison of raw z-scored activity indicated

that this faster ramp-up was due to a steepening of the slope rather than to a reduction in

absolute peak X_1 activity (Fig. 2j$_{ii}$, inset; Extended Data Fig. 4d, e$_{ii}$). This faster ramp-up
in starved mice mirrored the reduced latency from the first sniff to the first attack in this
condition (Fig. 1h, I; Extended Data Fig. 4e$_i$). Indeed, these two parameters were strongly
and significantly correlated both within and across mice (Fig. 2; Extended Data Fig. 4e,
f). Thus, 18-hr food deprivation caused a change in neural dynamics during the transition
from sniff to aggression, not a lowering of the threshold level of X_1 activity associated with
attack (Fig. 2l).

Our previous studies have shown that following ramp-up, activity in the line
attractor remains at a stable position during attack and then slowly decays back down the
attractor after the intruder is removed and fighting stops[46]. Importantly this decay
constant is highly correlated with the intensity of aggressiveness across individual
mice[46,48]. We therefore investigated whether the increased duration and frequency of
attack in 18 hr-starved mice might be reflected in an increased stability of the line attractor.
Indeed, activity in the X_1 dimension following the termination of attack decayed more
slowly in fasted than in fed mice (Fig. 2m, n), reflecting a significant increase in both the
absolute magnitude of the X_1 time constant, and in the X_1:X_2 time constant ratio (Fig. 2o;
Extended Data Fig. 4g). Consistent with this, the ACHWs of neurons strongly weighted
on the X_1 dimension were significantly longer in fasted than in fed mice (Fig. 2p, q, mean
ACHW: 11.6 ± 0.6s for fed state vs 14.9 ± 0.7s for fasted state, p***=0.0006, n=6 mice),
and were greater than in the bulk VMHvl^{Esr1} population (Fig. 2q vs. Extended Data Fig.
3j). Taken together, these data indicate that the effect of 18-hr fasting to increase
aggressive behavior is correlated with changes in two dynamic X_1 parameters: faster
ramp-up and slower decay along the attractor.

In 2D flow field maps of neural state space, under both conditions the trajectory of
the latent factor activity vector reached the end of the line attractor when attack
commenced (Fig. 2r$_{ii}$, s$_{ii}$). However, the initial trajectory was different with respect to the
X_2 dimension in fasted mice, initially following a path at an acute angle to the attractor
before relaxing to the line itself, rather than moving up the attractor as in fed mice (Fig. 2r
vs. 2s; Extended Data Fig. 4h). The raw activity and initial dynamics in the X_2 dimension
appeared similar in both conditions, although there was a trend to lower X_2 peak activity

in fasted mice (Extended Data Fig. 4c). Activity in X_2 may represent novelty or social

fear[46], and is known to interact with X_1[47]; it is possible that the strength of this interaction

is enhanced by starvation.

Prolonged fasting reveals a biphasic effect of food deprivation on the stability of VMHvl[Esr1] attractor dynamics

Changes in neural dynamic parameters and behavioral metrics observed between

ad libitum-fed and 18-hr fasted mice indicate that moderate food deprivation robustly

enhances both measures, consistent with the 'hangry' state described in humans[12,13] and

other species[7,8,9 ,15]. To reconcile this with reports that starvation suppresses aggression

in mice[6,14] and with our finding that prolonged fasting (40 hr) markedly reduces aggression

(Extended Data Fig. 1d), we next examined neural population dynamics under this latter

condition (Fig. 3a).

First, we confirmed that *Esr1*[Cre/+] mice implanted with a GRIN lens and miniscope

responded to 40-hr starvation like wild-type unoperated mice, exhibiting a marked

decrease in aggressive, but not investigatory, behaviors (Fig. 3b, c). rSLDS modeling

revealed that, in contrast to the 18-hr fasted condition (Fig. 3f$_i$-burgundy, g-blue), activity

projected onto the X_1 dimension in 40-hr fasted animals exhibited rapid decay following

the first sniffing bout (Fig. 3e, f$_{ii}$-burgundy, g-purple, h). Accordingly, the time constant of

the X_1 dimension was not significantly greater than that of X_2 dimension (Fig. 3i, inset),

and was markedly reduced relative to both the 18-hr fasted condition (Fig. 3i, j$_i$; 18-hr vs.

40-hr) and *ad libitum*-fed controls (Fig. 3j$_i$; 0 vs. 40-hr). The same was true for the ratio

between the time constants of X_1 and X_2 (Fig. 3j$_{ii}$).

In agreement with these changes in latent factor dynamics, analysis of ACHWs in

X_1-weighted neurons identified using the emission matrix demonstrated reduced

persistence and shorter decay times in 40-hr starved vs. the 18-hr fasted and fed states

(Fig. 3k). Concordantly, 2D vector flow-field visualizations of rSLDS models from 40-hr

fasted mice failed to exhibit a well-defined linear region of slow points (Fig. 3l, cf. Fig. 2r,

s). Collectively, these data suggest that in 40-hr fasted mice, the line attractor is either

absent or is considerably "leakier" than that in either *ad libitum*-fed or 18-hr fasted mice.

These findings reveal a biphasic, bi-directional effect of hunger on aggression, which is

reflected by a corresponding biphasic change in line attractor dynamics (Fig. 3m).

281   Titrated activation of hunger-promoting neurons modulates aggression and
282   VMHvl[Esr1] attractor dynamics, recapitulating effects observed during naturalistic
283   food deprivation.

Our results revealed a robust interplay between starvation and aggression at the

level of population dynamics in VMHvl[Esr1] neurons. We next investigated whether the

opposite-direction effects of food deprivation on aggressiveness at 18 vs. 40 hr reflected

a change in the effects of a graded hunger motivational state at different intensities, or

rather the gradual depletion of energy resources or weight loss after extended starvation.

To distinguish between these possibilities, we tested whether acute, graded activation of

hypothalamic 'hunger' neurons[50,54,67] at different intensities in *ad libitum*-fed mice could

recapitulate the starvation-induced biphasic effects of starvation on aggressive states and

population neural dynamics.

To this end, we employed titrated chemogenetic activation of AgRP-expressing

neurons in the arcuate nucleus (ARC[AgRP] neurons); these neurons promote a hunger drive

in response to interoceptive cues that signal reduced bodily energy state[50,52-54,68].

Previous studies have demonstrated that graded changes in the intensity of ARC[AgRP]

neuronal activation produced correspondingly graded increases in food intake[53,69].

Although strong activation of these neurons moderately affects aggression[6,14], whether

titrated activation can yield bi-directional effects at different intensities has not previously

been investigated. To test this, we systemically administered deschloroclozapine (DCZ),

a metabolically stable and fast-acting DREADD agonist, at different calibrated doses (0,

[saline control], 0.1, 0.5, 1.0 mg/kg)[70] on different days to *ad libitum*-fed AgRP[Cre/+] mice

injected with AAV-FLEX-hM3Dq-mCherry into the ARC 40 min prior to conducting RI

assays (Fig. 4a; see Methods).

At the lowest dose of DCZ (0.1 mg/kg), there was no significant effect on attack-

related parameters compared to the control condition; however, there was a marginal

reduction in the latency to initiate feeding, indicating the efficacy of chemogenetic

activation of ARC[AgRP] neurons even at this relatively low dose (Fig. 4b-d, 0.1mg/kg). In

contrast, at an intermediate dose (0.5 mg/kg), mice displayed a significantly shorter

latency to the first attack as well as a marked increase in the time spent attacking (Fig.
4b, c, 0.5mg/kg), resembling "hangry" mice. The latency to initiate feeding was further
reduced, resulting in virtually immediate engagement in feeding behavior upon food
presentation in the absence of an intruder male (Fig. 4d, 0.5 mg/kg). In contrast, at the
highest dose of DCZ tested (1 mg/kg), aggressive behaviors were markedly suppressed,
and animals exhibited an immediate initiation of feeding upon food presentation (Fig. 4b-
d, 1 mg/kg). Thus, titrated chemogenetic activation of ARC^{AgRP} neurons recapitulated the
biphasic, bi-directional effect of progressively increased durations of food deprivation on
aggression (Fig. 4b, c; see also Fig. 3b and Extended Data Fig. 1d).

Next, to assess whether and how the graded activation of ARC^{AgRP} neurons
modulates attractor dynamics in VMHvl^{Esr1} neurons, we combined miniscope imaging of
VMHvl^{Esr1} neurons with titrated chemogenetic activation of ARC^{AgRP} neurons (Fig. 4e, f).
Specifically, we expressed a Flp-dependent GCaMP8m calcium indicator in VMHvl^{Esr1}
neurons and a Cre-dependent FLEX-hM3Dq-mCherry virus in ARC^{AgRP} neurons of
AgRP$^{Cre/+}$; Esr1$^{Flp/+}$ double-transgenic mice (Fig. 4e). VMHvl^{Esr1} neural activity was
longitudinally recorded across multiple days under three experimental conditions: mice
were subjected to systemic administration of saline (control), 0.5mg/kg (medium), and
1mg/kg (high) doses of DCZ in a physiologically *ad libitum*-fed state, using a counter-
balanced design across conditions (Fig. 4f), and calcium signals were acquired during an
RI assay 40 minutes following drug administration. Social behaviors were measured in
synchronized video recordings (Extended Data Fig. 5a, blue and red rasters).

rSLDS models fit to VMHvl^{Esr1} neural population activity recorded at different DCZ
doses yielded consistently high cvR^2 values across all tested conditions (Fig. 4g). Notably,
quantitative changes in dynamic parameters of the two latent dimensions revealed by
rSLDS modeling during titrated activation of ARC^{AgRP} neurons closely mirrored the
biphasic dynamical changes observed under naturalistic food-deprivation conditions (Fig.
4h-i vs. 4k-l). Specifically, under control (saline-injected) conditions, activity along the X_1
dimension progressively ramped up before the initiation of the first attack (Fig. 4h$_i$;
Extended Data Fig. 5a-left, 5c-gray), similar to *ad libitum*-fed un-injected control mice (Fig.
4k$_i$). Activation of ARC^{AgRP} neurons at the medium DCZ dose, when mice showed the

shortest latency to attack behavior (Fig. 4b; 0.5 mg/kg), yielded more rapid ramping

followed by sustained activity in the X_1 dimension (Fig. 4h$_{ii}$-burgundy; Extended Data Fig.

5a-middle, 5b, c-d (pink), 5d-e), resembling the X_1 activity pattern in the 18-hr fasted

condition (Fig. 4k$_{ii}$). Aligning neural trajectories along the X_1 dimension to the onset of the

initial sniff revealed a significantly accelerated ramping rate in the medium-dose condition

compared to controls (Extended Data Fig. 5a; left vs. middle and 5c-e). Remarkably, the

latency to attack was almost perfectly correlated across mice with the time-to-peak of

projected X_1 activity in the medium-dose condition (Extended Data Fig. 4f; R^2 = 0.98,

p*=0.045). This correlation was even stronger than that observed under 18 hour of food

deprivation (R^2 = 0.85; Fig. 2k; Extended Data Fig. 4f-left), perhaps reflecting the more

precise control over hunger levels achieved by chemogenetic activation of ARC^{AgRP}

neurons.

In contrast, during chemogenetic activation of ARC^{AgRP} neurons at the highest

dose tested (1 mg/kg), rSLDS analysis revealed a pronounced reduction in the

persistence of activity along the X_1 dimension, reflected in a rapid decay following initial

sniff (Fig. 4h$_{iii}$-burgundy; Extended Data Fig. 5a-right, 5g-dark red). This rapid decay

resembled the faster dynamics observed in the prolonged starvation condition (Fig. 4k$_{iii}$),

and was reflected by a reduced magnitude of the X_1 time constant remarkably similar to

that seen under 40 hr starvation (Fig. 4i, l; Extended Data Fig. 5l). Notably, both the

persistence of X_1 activity, quantified as the area under the curve (AUC) following the initial

sniff, and the ACHWs of X_1-weighted neurons, were significantly diminished in the high-

dose DCZ condition, compared to the medium-dose (0.5 mg/kg) condition (Fig.4j;

Extended Data Fig. 5g, h, k). These dose-dependent biphasic effects were further

underscored by changes in the ratio of the X_1 to X_2 time constants (Extended Data Fig.

5i, j, m), highlighting a graded, biphasic modulation of attractor stability by scaled hunger

levels.

Consistent with the observed DCZ dose-dependent changes in these fit rSLDS

model parameters, neural trajectories visualized in a two-dimensional flow-field state

space under the medium-dose condition closely resembled those observed after 18 hours

of fasting, with prominent line attractors in both conditions (Extended Data Fig. 6a vs. 6b).

In contrast, the trajectories under the high-dose condition exhibited disrupted attractor
dynamics reminiscent of those following 40 hours of fasting, characterized by a loss of
clearly defined linear regions of slow points (Extended Data Fig. 6c vs. 6d). Changes in
the ACHWs of individual X_1 dimension-weighted neurons under titrated chemogenetic
AgRP neuron activation similarly paralleled the changes observed under naturalistic food
deprivation states (Fig. 4j vs. 4m).

Thus, graded activation of ARC^{AgRP} neurons in *ad libitum*-fed mice reproduced the
bi-phasic changes in both aggressive behavior and the dynamics of VMHvl^{Esr1} neuronal
activity observed with different durations of food deprivation (Fig. 4n; Extended Data Fig.
6e). These data argue against the idea that the reduced aggression observed after 40 hrs
of starvation is due simply to energy depletion or weight loss and imply that increasing
intensities of a unitary starvation state are converted into opposite-direction modulation
of aggressiveness and line attractor properties at distinct thresholds. They further suggest
that the VMHvl line attractor constitutes a key integrative node where metabolic and
motivational signals converge to regulate aggressiveness, likely through state-dependent
modulation of underlying population dynamics. While we cannot formally exclude that
hunger-induced changes in line attractor dynamics might be a consequence rather than
a cause of changes in aggressive behavior, this seems unlikely given that the line attractor
is present in mice passively observing, as well as actively engaging in, attack behavior[47],
and that it persists in 'hangry' mice in which attack is interrupted by feeding (see below).

Increased line attractor stability in 'hangry' mice maintains aggressiveness during
feeding

The above results establish that a graded hunger state can either enhance or
suppress aggressiveness and line attractor dynamics, depending on its intensity. Given
that aggression is energetically costly[71] and mutually exclusive with feeding, these
findings prompted us to ask two related questions: 'Why does an intermediate level of
hunger elevate aggression?', and 'Why is this increase in aggressiveness encoded in the
enhanced stability of a line attractor, rather than simply by an increased activity in
aggression-promoting neurons?' To tackle these questions, we further examined attractor
dynamics under conditions in which 18-hr fasted animals were allowed to choose

between feeding and attacking an intruder. To this end, following an approximately 2-min
RI test to assess the resident's baseline level of aggressiveness, we introduced a chow
pellet without removing the intruder (Fig. 5a). After imaging neural activity and observing
behavior for two minutes in the presence of both the food and the intruder, we removed
the intruder but left the food pellet in place (to determine whether the resident was satiated
or still hungry). This design allowed us to examine the animal's behavioral choices under
conditions of competing hunger and aggressive drive states, with targets of both
consummatory behaviors concurrently provided.

Following the introduction of the chow pellet, 'hangry' mice immediately stopped
fighting, investigated the pellet, and ate (Fig. 5b, d-left). In contrast, relatively little feeding
was observed in *ad libitum* fed animals, as the chow pellet only yielded brief interruptions
of attack (Fig. 5b, c). In the 18-hr fasted mice, following a period of feeding (~100 s), 67%
of the fasted mice resumed attacking the intruder (Fig. 5d-right; Extended Data Fig. 7a,
b-pie chart). However, their latency to resume attack was marginally longer than in the *ad*
libitum-fed control condition (mean latency to resume attack after the offset of the first
food sniff (s): 137 ± 26 s (fasted) vs. 94 ± 24 s (fed), p=0.06) (Fig. 5d; Extended Data Fig.
7b). Following the initial re-attack, 18-hr fasted mice resumed feeding and continued with
interspersed feeding and attack bouts (Fig. 5d-right; Extended Data Fig. 7a). Overall, the
fasted mice spent far more time feeding than attacking (percent time spent eating vs.
attacking in fasted state: 32.7 ± 4.42 % (eating) vs. 3.37 ± 0.67 % (attacking), ****p<0.001;
in fed state: 3.2 ± 3.7 % (eating) vs. 3.7 ± 1.3 % (attacking), p=0.882, Fig. 5e; Extended
Data Fig. 7a-right). Nevertheless, under these conflicting conditions mice did not achieve
satiety, as indicated by extensive feeding following removal of the intruder (Fig. 5f, yellow
raster). These findings reveal a dynamic and hierarchical interplay between two
competing motivational states and suggest that mice are willing to delay or sacrifice full
repletion of their energy reserves in order to defend their food resource from a competitor
male.

We next sought to determine how neural activity and dynamics in VMHvl[Esr1]
neurons might be modulated during the observed dynamic switching between fighting
and feeding. Unexpectedly, hierarchical clustering as well as choice probability analysis

of single VMHvl^{Esr1} neuron activity revealed a robust population of eating-tuned neurons in 18hr fasted mice (Fig. 5f-h). Consistent with this observation, a larger fraction of variance in neuronal activity could be explained by a behavior-weighted GLM in fasted mice during interactions with food and a male, compared to GLMs fit to the same mice in the absence of food but presence of male (mean cvR^2 in fasted mice with food: 27% variance explained, Extended Data Fig. 7c$_i$; mean cvR^2 in fasted mice without food: 17% of variance explained, Extended Data Fig. 3b, lower), likely reflecting the behavior-locked activity of the eating-tuned population (see below; Fig. 5h). Nevertheless, the addition of a cell-coupling term still increased the variance explained by GLMs in the presence of food (mean cvR^2: 0.27 with only behavioral regressors, cvR^2: 0.52 with behaviors and cell-coupling, Fig. 5i; Extended Data Fig. 7c$_{ii}$). This suggests that local functional connectivity between neurons - and therefore potentially neural dynamics - influences population activity in this paradigm as well.

To directly examine neural dynamics in this competition paradigm, we fit rSLDS models to VMHvl^{Esr1} activity. In this condition, models with three dimensions instead of two explained a greater fraction of neural variance in data (66.3 ± 4% variance explained for the 3D model vs. 44.1 ± 2% variance explained for the 2D model, Extended Data Fig. 7d). To understand the behaviors represented by these three latent factors, we analyzed their projected time-varying activity during sniffing, attack, and eating (Fig. 5j; Extended Data Fig. 7e, f). The X_1 dimension exhibited ramping activity that peaked near the attack onset and persisted thereafter (Fig. 5j, k, l$_i$, m$_i$-burgundy; Extended Data 7e, f, X_1), as previously described[46]. Interestingly, despite the switch of overt behavior from attacking to eating, the level of activity in the X_1 dimension remained stable and elevated during food sniffing and consumption (Fig. 5j, k, l$_{ii-iii}$, m$_{ii-iii}$, burgundy; Extended Data Fig. 7e, f, X_1). Notably, when animals resumed attacking, activity in the X_1 dimension was similar to that observed during the initial attack (Fig. 5l$_{iv}$, m$_{iv}$; Extended Data Fig. 7e, f, X_1 and 7i). By contrast, activity in the X_2 dimension declined following the initial male interaction and remained relatively low throughout aggression, feeding and re-attack (Fig. 5j, k, l$_{i-iv}$, m$_{i-iv}$-gray; Extended Data Fig. 7e, f, X_2).

In contrast to these first two dimensions, the X_3 dimension, enriched in food-
modulated neurons (Fig. 5j, X_3), displayed little activity during male interactions before
the delivery of the food pellet, but exhibited time-locked, transient increases in activity
during feeding bouts (Fig. 5l$_{ii}$-arrowhead, 5m$_{ii}$-green; Extended Data Fig. 7e, f, X_3).
Following the offset of eating, the X_3 dimension displayed rapid decay, unlike the slow
decay observed in the X_1 dimension (Fig. 5l$_{iii}$-arrowhead, n), reflecting distinct dynamics
across these two dimensions of activity.

These results indicate that activity in the X_1 line attractor-aligned dimension
remained stably elevated as the animal switched back and forth between attacking and
eating (Extended Data Fig. 7g). Indeed, a decoder trained on the activity of the X_1
dimension was unable to distinguish video frames containing attack vs. eating (Fig. 5o),
whereas a decoder trained on the activity of the X_3 dimension robustly distinguished
attack vs eating frames (Extended Data Fig. 7h). In line with this population-level
dissociation, neurons with strong weights onto the X_3 dimension exhibited significant
tuning for eating, whereas neurons contributing to the X_1 and X_2 dimensions were
preferentially tuned to male-directed behaviors (Extended Data Fig. 7i, j).

To visualize the dynamics of these three dimensions in neural state space, we first
plotted the fit rSLDS state-space model as a vector flow field spanned by the X_1-X_2
dimensions. In this space, we observed that the population vector remained in the line
attractor during bouts of eating as well as attack (Extended Data Fig. 8a-d). In contrast,
the fit vector flow field spanned by the X_1-X_3 dimensions revealed that the population
vector displayed movements orthogonal to the line attractor and parallel to the X_3
dimension during eating but returned to the line attractor immediately when the animals
switched back to attack (Extended Data Fig. 8e-h).

Together, these findings revealed that neural population dynamics in the VMHvl[Esr1]
neurons of mice in a behavioral choice paradigm exhibited a persistently elevated
component of activity in the X_1 (line attractor) dimension, despite repeated switches
between attack and eating. Transitions to eating engaged an orthogonal dimension (X_3),
which (in contrast to X_1) displayed rapid decay following the offset of feeding. As attack

resumed following such feeding bouts, activity in the line attractor dimension dominated
over that in the orthogonal dimensions (X_2 and X_3) (Fig. 5p-r).

DISCUSSION

While VMHvl is well-known to regulate both social behaviors[20,22,72] and feeding[73,74],
relatively few studies have investigated how these two functions influence each other[21]
and none has done so at the level of neural population activity. Here we have investigated
how aggressiveness and neural dynamics are influenced by hunger in VMHvl. We find
that starvation exerts bi-phasic, opposite-direction effects on aggression depending on
the duration of food deprivation[6,14,15], and that these bi-phasic effects are reflected in bi-
phasic changes in line attractor dynamics[46] rather than in overall levels of activity among
VMHvl^{Esr1} neurons. For example, our analysis suggests that 'hangry' mice do not have a
"shorter fuse" than fed mice, as intuition might suggest; rather, their "fuse" is the same
length, but burns faster (increased ramping rate from baseline to peak in the X_1
dimension). Together, our observations reveal how population neural dynamics that
encode aggressiveness, an affective or emotional internal state[75], can be modified by a
competing homeostatic physiological drive state[76,77].

Importantly, the bi-phasic effects of food deprivation on aggressiveness and line
attractor dynamics could be replicated by acute, titrated chemogenetic activation of
ARC^{AgRP} neurons[52,53] in sated mice. This finding argues that these bi-directional effects
reflect different intensities of a graded hunger state[5,78], and that the loss of
aggressiveness after 40 hrs of starvation[5,6,14] is not due simply to gradual depletion of
energy reserves or to weight-loss. These observations make sense from an ecological
perspective[79]. In this view, the level of risk the animal is willing to tolerate scales with the
intensity of its starvation state: if moderately hungry, the animal will fight to protect its food
supply, risking further energy depletion (and injury or death if defeated). With extended
starvation, however, the animal prioritizes food consumption, during which time it is
vulnerable to attack. The circuit-level mechanisms whereby continuous increases in the
level of hunger cause opposite-direction effects on aggressiveness at different thresholds
are likely complex[21,80], and remain to be investigated.

Why should the competition between hunger and aggressiveness be reflected by
changes in line attractor dynamics? An attractor provides a region of stability in neural
state space, to which neural activity rapidly returns if subjected to an off-manifold
perturbation[40]. When "hangry" animals engaged in fighting were presented with food
pellets, they initially switched from fighting to feeding. Although neural population activity
moved out of the attractor during food consumption, activity in the attractor dimension
remained elevated. Following such feeding bouts, activity rapidly returned to the line
attractor dimension as attack resumed (Fig. 5r). These observations suggest a potential
adaptive role for the VMHvl line attractor, namely, to keep hungry animals primed for
aggression while feeding in the presence of an intruder. At the manifold level[37,38], we
speculate that the "attractive" nature of the integration dimension may provide a
counterpoint to the strong motivation to feed, thereby mediating a delicate balance
between these competing drives. How this balance is computed and read out to control
behavior will be an important question for future investigation.

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Author contribution

J.K. and D.J.A. conceived the project. J.K. performed all experimental work with help from
S.H., A.V., and M.L. J.K. and A.N. performed computational analyses. N.C. and A.N.

developed data analysis pipelines with help from J.X. J.K., A.N., and D.J.A. analyzed and

interpreted the data and co-wrote the manuscript. D.J.A. supervised the project.

Competing interests

The authors declare no competing interests.

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METHODS

Animals

All experimental procedures involving the use of live mice or their tissues were carried out following NIH guidelines and approved by the Institute Animal Care and Use Committee (IACUC) and the Institute Biosafety Committee (IBC) at the California Institute of Technology (Caltech). All mice in this study, including wild-type and transgenic mice, were bred at Caltech or purchased from Charles River Laboratory. Group housed C57BL/6N female or singly housed male mice (2-5 months) were used as experimental mice. *Esr1^{cre}* mice, *Esr1^{flp}* mice were backcrossed into the C57BL/6N background (>N10) and bred at Caltech. Heterozygous *Esr1^{cre}* or double heterozygote *Esr1$^{flp/+}$AgRP$^{cre/+}$* mice were used for cell-specific targeting experiments and were genotyped by PCR analysis using genomic DNA from tail tissue. All mice were housed in ventilated micro-isolator cages in a temperature-controlled environment (median temperature 23°C, humidity 60%), under a reversed 11-h dark–13-h light cycle, with *ad libitum* access to food and water. Mouse cages were changed weekly.

Housing conditions for social and sexual experience

All male C57BL/6N mice used in this study were socially and sexually experienced. Mice aged 8–12 weeks were initially co-housed with a female BALB/c mouse for 1 week and were screened for male-typical social behaviors. Mice that showed both mounting towards females and attacking towards males during a 30-minute resident intruder assay were selected for surgery and subsequent behavior experiments. From this point forward, these male mice were always co-housed with non-pregnant female BALB/c mice.

Stereotaxic Surgeries

Virus injection and implantation were performed as described previously[33,37]. Briefly, animals were anesthetized with isoflurane (5% for induction and 1.5% for maintenance) and placed on a stereotaxic frame (David Kopf Instruments). The virus was injected into the target area using a pulled-glass capillary (World Precision Instruments) and a pressure injector (Micro4 controller, World Precision Instruments), at a 20 nl min^{-1} flow

rate. The glass capillary was left in place for ten minutes following injection before
withdrawal. Integrated GRIN Lenses (Inscopix) were slowly lowered into the brain and
fixed to the skull with dental cement (Metabond, Parkell). After virus injection and lens
implantation, males were co-housed with an ovariectomized or non-pregnant female
mouse. Four to six weeks after lens implantation, mice were head-fixed on a running
wheel, and a miniaturized micro-endoscope (nVista, Inscopix) was lowered over the
implanted lens until GCaMP-expressing fluorescent neurons were in focus.

Virus injection and GRIN lens implantation

The following AAVs were used in this study, with injection titers as indicated. Viruses with
a high original titer were diluted with clean PBS on the day of use. AAV1-EF1a-FLEX-
GCaMP8m (~2.3 x10^{12}vg/ml, Addgene), AAVdj-hSyn-fDIO-GCaMP8m (~2.0x10^{12} vg/ml,
Janelia Vector Core), and AAV8-DIO-hM3Dq (4x10^{12} vg/ml, Addgene).

Stereotaxic coordinates for the viral injection (unless specified):
VMHvl, AP: −1.6, ML: ±0.78, DV: −5.7 (from the skull surface)
ARC, AP: -1.7, ML: ±0.25, DV: -5.85 mm (from the bregma)
Stereotaxic injection coordinates were based on the Paxinos and Franklin atlas. GRIN
lens implantation: VMHvl, AP: −1.6, ML: −0.76, DV: −5.55 (⌀0.6 × 7.3 mm GRIN lens).

Behavioral assays

Prior to resident-intruder (RI) assays, male mice were co-housed with females to have
sexual experience for at least one week. Before the assay, cohoused females were
removed from the home cage for at least two days. Male mice were acclimated to the
behavioral room with a dimmed red light for two consecutive days, followed by a third day
of habituation for five minutes of interaction with a male Balb/c mouse to reduce any
novelty. The day before the RI assay, mice were separated into 'fed' or 'fasted' cohorts,
counter-balanced for the order of conditions. At the onset of fasting (food removal), every
mouse in the relevant cohort was singly transferred into a new home cage with fresh
bedding. On the day of the RI assay, mice were habituated to the behavior chamber for
10 minutes, followed by a 'baseline' for 5 minutes. A novel Balb/c male (or for mating
assays, a sexually experienced/hormonally primed female mouse) was introduced, and

the RI session continued for 5 or 10 minutes. For the choice assay, following an initial 2
min interaction with a male intruder either a 2.5-4g normal chow pellet (or, as a control,
the cap of a 15ml Falcon tube) was dropped into the home cage, leaving the intruder in
place. After two minutes of observation, the intruder was removed and the test mouse left
alone with the food pellet for an additional 5-10 minutes to assess its feeding behavior.

Behavior recording

All behavioral experiments were performed in conventional mouse housing cages (the
resident mouse's home cage) under red lighting, using the previously described behavior
recording setup [81]. The behavior video's top and front views were acquired at 30 Hz using
StreamPix9 (Norpix) video recording software.

Behavior Annotations

Behavior videos (top and side views) were manually annotated using a custom MATLAB-
based behavioral annotation interface called BENTO[57].

We manually annotated the following resident male behaviors:

During male-male interactions: sniffing the male (body, genital, and face), dominance
mounting, and attack. For analysis of the imaging experiment, we also detailed the
intruders' behaviors, including exploration of the cage, immobility, and defensive postures
(exposing their abdominal parts while standing). During male-female interactions, sniffing
the female (body, genitals, and face), mounting, and intromission were scored. During
male-food interaction, sniffing food and eating were scored.

Chemogenetic activation
Behavioural tests were performed at three day intervals, at minimum. The order and
number of mice receiving saline or DCZ (Sigma) were counterbalanced across different
conditions. DCZ was dissolved in DMSO and further diluted in saline; DCZ (0.1, 0.5,
1.0 mg/kg of body weight) or saline (control) was intraperitoneally (i.p.) injected 40-50 min
before behavioral tests.

Chemoscope imaging

For experiments combining miniscope imaging with chemogenetic manipulations
("Chemoscope"[82]), to minimize population activity changes associated with stress from
i.p. injections, a series of habituation sessions was performed every two consecutive days
before any test conditions used for analysis. Mice were injected with 10ul/g (body weight)
of saline (control) and returned to their home cage for 40-50 min before imaging[82]. On the
test day, mice were injected with control or 10ul/g of different doses of DCZ (0.5 vs
1.0mg/kg). The order and number of mice in each condition were randomized, and other
conditions were performed at 2-3 days intervals. On the day of imaging, mice were
injected 40-50 mins before the RI assay.

Miniscope data acquisition and extraction

On the day of imaging, mice were habituated for at least 10 minutes after installing the
miniscope (Bruker, Inc.) in their home cage before the start of the behavior tests. Imaging
data were acquired at 30 Hz with spatial down sampling (2); light-emitting diode power
(0.2) and gain (3–6) were adjusted depending on the brightness of GCaMP expression
as determined by the image histogram according to the user manual. A transistor–
transistor logic (TTL) pulse from the Sync port of the data acquisition box (DAQ, Inscopix)
was used for synchronous triggering of StreamPix9 (Norpix) for video recording. Imaging
sessions typically lasted 30 mins per day. Preprocessing and motion correction were
performed using Inscopix Data Processing Software. Briefly, the raw imaging data were
spatially sampled twice, motion corrected, and temporally downsampled to 10 Hz, and
then exported as a .tiff image stack. A spatial band-pass filter was then applied to remove
the out-of-focus background. After preprocessing, calcium traces were extracted and
deconvolved using the CNMF-E large data pipeline[83] with the following parameters:
patch_dims = [32, 32], gSig = 3, gSiz = 13, ring_radius = 15, min_corr = 0.7-0.8, min_pnr
= 8. Every extracted unit's spatial and temporal components were carefully inspected
manually (signal-to-noise ratio, peak-to-noise ratio, size, motion artifacts, decay kinetics,
and so on), and outliers (apparent deviations from the normal distribution) were discarded.
The extracted traces were then z-scored before further analysis.

Longitudinal imaging data extraction and preprocessing

We imaged the male mice implanted with a GRIN lens for multiple days under varying durations of food deprivation in a non-consecutive manner with two to three days' intervals. On the day of imaging, we compared the field of view with a reference mark to ensure the accuracy of registration of the spatial FOV across different days. Miniscope data was selected and concatenated into one .isxd file. Data was preprocessed, and the traces were extracted as described in the last section. The extracted traces were z-scored and split into multiple traces for individual days[59]. If two imaging sessions were compared directly, the cell registration algorithm[83] in the CIAtah was used to extract traces in the registered cells.

Immunohistochemistry

For Fig.4a, animals were anesthetized with isoflurane 90 mins after 1 mg/kg DCZ treatment and cordially perfused with 30 ml of cold 4% PFA following 30 ml of 0.9% saline. Brains were post-fixated for 4 hrs in 4% PFA at 4°C and then transferred to 30% sucrose in PBS. Brains were coronally sectioned at 60 μm using a Leica cryostat. The sectioned brains were washed with PBS for 10 mins and blocked with 2 % normal donkey serum in 0.2% PBST for 1 hr at R.T. Primary antibodies, goat anti-cFos (1:200, Santa Cruz, sc 52-g), mouse anti-NPY (1:1000, Santa Cruz, sc-133080), in the blocking solution (2% NDS in 0.2% PBST-Triton X-100) were incubated at 4°C for 72 hours. The sections were washed with PBS (3 x 15 mins), followed by incubation of the second antibody, donkey anti-mouse Alexa 647 (1:500, Life Technologies, A21207) or donkey anti-goat Alexa 488 (1:500, Life Technologies, A11055), for 1 hr at RT. Then they were washed with PBS (2 x 15 mins), stained with DAPI (1:10000) for 6 mins, and mounted with DAKO mounting medium. Confocal images were captured with an Olympus microscope.

Data Analysis |

Calculation of pixel changes and pose estimation using MARS

Pose estimation was performed using MARS[57] to identify specific body parts ("keypoints")

of the resident mouse and the intruder mouse during behavioral assays. After identifying

keypoints, pixel changes were computed to quantify pose dynamics during behavior bouts,

such as sniffing or attack. Specifically, pixel change was calculated within a defined

region—a square measuring 20x20 pixels—surrounding each identified keypoint on the

resident mouse. This calculation was performed on a frame-by-frame basis throughout

the duration of each bout of sniffing or attack behavior. This metric of pixel change thus

provides a quantitative measure of pose dynamics and movement intensity localized to

each relevant body part, allowing comparisons of these parameters between fed and

fasted conditions.

Choice Probability (CP)

Choice probability (CP) analysis was performed as previously described[33,55] to quantify a

neuron's selectivity or "tuning," defined here as the ability to discriminate between two

behavioral conditions based on single-cell activity[84]. For each neuron, the CP was

calculated by constructing histograms of its $\Delta F(t)/F0$ activity values during the two

conditions of interest. These histograms were compared to generate a receiver operating

characteristic (ROC) curve, from which CP was determined by calculating the integral of

the area under the curve (AUC). CP values range from 0 to 1, with 0.5 representing

chance-level discrimination. To assess statistical significance, we performed a shuffle-

based permutation test by randomizing the timing of behavioral events across the two

conditions and recalculating CP 100 times. Observed CP values were considered

significant if they exceeded two standard deviations (2σ) above the mean shuffled CP

distribution and additionally surpassed an absolute CP threshold of 0.75, consistent with

established criteria[33,55]. Colored bars indicate neurons exhibiting robust and statistically

significant CP values, whereas grey bars represent neurons whose CP either fell below

the 2σ significance threshold or failed to exceed the established CP criterion of 0.75.

Generalized linear model (GLM)

To predict neural activity from behavior, we trained generalized linear models to predict

the activity of each neuron k, as a weighted linear combination of male-directed

behaviors (male sniffing and attack behaviors) or food-directed behaviors (food sniffing
and eating behaviors), as follows:

$$y_k(t) = \vec{x}(t)\vec{\beta} + \varphi$$

Here, $y_k(t)$ is the calcium activity of neuron k at time t, $\vec{x}(t)$ is a feature vector of 3 binary
male behaviors at time lags ranging from t-D to t where D = 10s. $\vec{\beta}$ is a behavior filter
that describes how a neuron integrates stimulus over a 10s period. φ is an error term.
The model was fit using 10-fold cross-validation with ridge regularization, and model
performance is reported as cross-validated R^2 (cvR^2). To account for cell-cell interactions
within the network, we also used the activity of simultaneously imaged neurons as
regressors in addition to behavior, as previously described[59].

Dynamical system models of neural data

rSLDS models fit the neural data as previously described[46]. In brief, rSLDS is a generative
state-space model that decomposes nonlinear time-varying data into discrete states,
each with simple linear dynamics. The model describes three sets of variables: discrete
states (z) and latent factors (x) that represent the low-dimensional features from the
population activity of recorded neurons (y). While the model can also allow for the
incorporation of inputs based on behavior features, such external inputs were not included
in the first analysis.

The model is formulated as follows: At each time point, there is a discrete state $z_t \in$
$[1, ..., K]$ that depends recurrently on the continuous latent factors (x) as follows:

$$p(z_{t+1} \mid z_t = k, x_t) = \text{softmax}\{R_k x_t + r_k\} \qquad (1)$$

971   where $R_k \in \mathbb{R}^{K \times K}$ and $r_k \in \mathbb{R}^K$ parameterizes a map from the previous discrete state and

972   continuous state to a distribution over the following discrete states using a softmax link
973   function. The discrete state z_t determines the linear dynamical system used to generate
974   the latent factors at any time t:

$$x_t = A_{z_t} x_{t-1} + b_{z_t} + \epsilon_t \qquad (2)$$

976 where $A_k \in \mathbb{R}^{d \times d}$ is a dynamics matrix and $b_k \in \mathbb{R}^D$ is a bias vector, where D is the

977 dimensionality of the latent space and $\epsilon_t \sim N(0, Q_{z_t})$ is a Gaussian-distributed noise (aka

978 innovation) term where $Q_{z_t} \in \mathbb{R}^{D \times D}$.

979 Lastly, we can recover the activity of recorded neurons by modeling activity as a linear,

980 noisy Gaussian observation $y_t \in \mathbb{R}^N$ where N is the number of recorded neurons:

$$y_t = Cx_t + d + \delta_t \tag{3}$$

982 For $C \in \mathbb{R}^{N \times D}$ and $\delta_t \sim N(0, S)$, a Gaussian noise term. Overall, the system parameters

983 that rSLDS needs to learn consist of the state transition dynamics, the library of linear

984 dynamical system matrices, and the neuron-specific emission parameters, which we write

985 as:

$$\theta = [(A_k b_k, Q_k, R_k, r_k)_{k=1}^K, C, d, S] \tag{4}$$

We evaluate model performance using both the evidence lower bound (ELBO) and the

forward simulation accuracy (FSA) previously described[46] and by calculating the variance

explained by the model on the data. Briefly, given observed neural activity in the reduced

neural state space at time t, we predict the trajectory of population activity over an ensuing

short time interval Δt using the fit rSLDS model, then compute the mean squared error

(MSE) between that trajectory and the observed data at time t+ Δt. This MSE is computed

across all dimensions of the reduced latent space and repeated across cross-validation

folds. This error metric is normalized to a 0-1 range in each animal across the holding to

obtain a bounded measure of model performance. The FSA can intuit where model

performance drops during the recording. In addition to MSE, we also calculate the

Pearson's correlation coefficient (R^2) between the predicted and observed data for each

dimension following the forward simulation. By taking the average correlation coefficient

across dimensions, we can obtain a quantitative estimate of variance explained by rSLDS

on observed data.

The number of states and dimensions used for the model is determined using 5-fold
cross-validation. Visualization of the dynamical system using principal components
analysis is performed as described previously[46].

Code used to fit rSLDS on neural data is available in the SSM package:
(https://github.com/lindermanlab/ssm)

Estimation of time constants

1007 We estimated the time constant of each dimension of linear dynamical systems using
1008 eigenvalues λ_a of the dynamics matrix of that system, derived previously[40] as:

$$\tau_a = \left| \frac{1}{\log(|\lambda_a|)} \right| \tag{5}$$

Calculation of line attractor stability

1011 As a quantitative measure to estimate the variance of approximate line-attractor
1012 dynamics, we calculated a log 2 ratio between time constants from X_1 and X_2
1013 dimensions as previously defined (sometimes referred to as the "line attractor score")[46-
1014 48,59] as:

$$log_2 \frac{t_n}{t_{n-1}}$$

1016 where t_n and t_{n-1} are the first and second largest time constants of the dynamics
1017 matrix.

Correlation of time-to-peak of integration dimension and latency to first attack

1019 We estimated the linear correlation between the time to peak of the integration dimension
1020 or the time to initiate the first attack behavioral action from the time of initiation of sniffing
1021 the intruder.

Calculation of auto-correlation half-width

1023 We computed autocorrelation half-widths by calculating the autocorrelation function for
1024 each neuron's time series data (y_t) for a set of lags as described previously[22]. Briefly, for
1025 a time series (y_t), the autocorrelation for lag k is:

$$1026 \qquad\qquad r_k = \frac{c_k}{c_0}$$

1027   where c_k is defined as:

$$1028 \qquad\qquad c_k = \frac{1}{T} \sum_{t=1}^{T-k} (y_t - \bar{y})(y_{t+k} - \bar{y})$$

1029   and c_0 is the sample variance of the data. The half-width is found for each neuron as the

1030   point where the autocorrelation function reaches a value of 0.5.

1031   Decoding of behaviors from the rSLDS dimensions

To evaluate whether the integration dimension (X_1) or X_3 dimensions could discriminate

between attack and eating behaviors, we trained a frame-wise decoder as previously

described [46,55]. Briefly, behavioral "trials" were constructed by concatenating behavioral

bouts separated by less than five seconds. We then trained a linear support vector

machine (SVM) classifier to determine an optimal decoding threshold for distinguishing

the normalized integration dimension signal[46] during frames associated with attack versus

eating behaviors. For shuffled control data, behavioral annotations were randomized

across bouts within each trial to disrupt genuine correlations, with this shuffling procedure

repeated 20 times per intruder and per mouse. Decoder performance was quantified

using the F1 score, averaged across held out "trials" for each animal. Additionally, to

rigorously control for potential artifacts arising from slow decay dynamics in the integration

dimension, we implemented a permutation test inspired by previous studies[46]. Specifically,

a decoding threshold obtained from one mouse was applied to the integration dimension

data of all other mice. High performance under this cross-animal decoding paradigm

would indicate that decoding accuracy reflects robust behavioral discriminability rather

than spurious correlations due to slow drifts in neural activity.

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1049   Quantification and statistical analysis

All statistical analyses were performed with GraphPad Prism 9.0.2. We conducted

unpaired two-tailed t-tests to compare two groups that present the normal distribution. In

the experiments with paired samples, we used the Wilcoxon matched-pairs signed test

or paired t-test. In the experiments with non-paired samples, we used the Mann–Whitney

U test. For multiple comparisons between the groups representing the normal distribution,

one-way ANOVAs followed by Holm Sidak's post hoc test were performed. The data are

presented as the mean ± SEM. One-way or two-way ANOVA tests were followed by Holm

Sidak's post hoc test. The significance threshold was held at a = 0.05, two-tailed (not

significant (ns), $p > 0.05$; $*p < 0.05$; $**p < 0.01$; $***p < 0.001$; $****p < 0.0001$.

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1060   **Reporting summary**

1061   Further information on research design is available in the Nature Research Reporting
1062   Summary.

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1064   **Data Availability**

1065   The data used in this study are available at the following URLs: (TBN on acceptance).

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1067   **Code Availability**

1068   Code for analysis can be found at https://github.com/lindermanlab/ssm. The supporting
1069   analysis code will be made available in DANDI upon publication.

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Fig. 1 Moderate food deprivation enhances territorial aggression in male mice

Territorial aggressive behaviors during male-male interaction under fed vs. 18-hr fasted states

a resident-intruder (RI) assay

b resident: C57B6/N
ad-lib fed vs 18hrs fasted

Increase in aggressive behaviors captured by pose estimation in 18 hr fasted states compared to *ad-lib* fed control

Fig. 1 | Moderate food deprivation enhances aggression in male mice.

(**a**) Schematic of resident-intruder (RI) assay for male-male interactions following *ad libitum*-fed or 18-hr fasting of the resident.

(**b**) Schematic of behavioral paradigm to compare aggressive behaviors across different energy states. The order of fed vs. fasted states was counter-balanced across cohorts, with a 2-day interval between conditions (Methods).

(**c-f, h**) Quantification of aggression parameters: (**c**) time spent in attack (%); (**d**) number of attack bouts/min; (**e**) average attack duration; (**f**) inter-bout-interval; and (**h**) latency to the first attack.

(**g**) Cumulative probability of re-attack after the onset of the first attack bout, across animals (n = 12 mice).

(**i**) Empirical cumulative distribution function (ECDF) plot showing latency to the first attack across the *ad libitum*-fed (brown) vs 18-hr fasted state (blue). Data scaled to 100%.

(**j**) Schematic illustrating unsupervised analysis of pose estimation features (Methods). The pixel change value associated with the resident mouse during each behavioral bout was computed for each mouse and compared across fed vs 18-hr fasted conditions.

(**k-l**) ECDF plots for pixel changes across fed vs. 18-hr fasted states during attack bouts (**k**), and during sniffing bouts (**l**). Bar graphs quantifying the mean pixel change across energy state from 6 mice (right).

$p<0.01$, ***$p<0.001$; ns, not significant. For all figure panels, data are mean ± SEM (n=6 mice in this and all figures unless otherwise indicated). See also **Extended Data Fig. 1.

Fig. 2 Moderate fasting enhances ramping and persistence in a VMHvl^Esr1 latent slow mode

Longitudinal imaging of VMHvl^Esr1 neurons

VMHvl^Esr1 neural activity with male intruder

Population dynamics of aggressive state-encoding VMHvl^Esr1 neurons under fed vs. 18 hr fasted states

Steeper ramping of VMHvl^Esr1 population dynamics is correlated with shorter latency to attack in 18 hr fasted state

Stability of VMHvl^Esr1 neural population dynamics under fed vs. 18 hr fasted states

Fig. 2 | Moderate fasting enhances ramping and persistence in a VMHvl^{Esr1} latent slow mode.

(**a**) (left) Imaging preparation and (right) representative histological section showing GCaMP8m expression (green) and GRIN lens implantation site.

(**b**) Representative imaging planes from longitudinal *in vivo* calcium imaging; color code indicates energy state (above) and mouse number for analysis (below).

(**c-d**) Rasters of VMHvl^{Esr1} neuron activity and resident behavior from a representative fed (**c**) or 18-hr fasted (**d**) mouse, aligned to intruder entry. "fed" and "fasted" above the baseline raster indicate pre-trial treatment.

(**e**) rSLDS model performance as cvR^2 for *ad libitum*-fed and 18-hr fasted conditions.

(**f-g**) Activity of rSLDS latent dimensions aligned with behaviors in a representative *ad libitum*-fed (**f**) and 18-hr fasted (**g**) mouse. Burgundy and gray curves indicate the X_1 and X_2 dimensions, respectively.

(**h-i**) Behavior-triggered average (BTA) of rSLDS dimensions (X_1-burgundy, X_2-gray) aligned to the first sniffing bout in the fed (**h**) or 18-hr fasted (**i**) states across mice (n = 6 mice).

(**j**) BTA of X_1 dimension aligned to first attack in 18-hr fasted vs. fed states (n = 6 mice). Inset: Slope of the ramping segment from (**j$_{ii}$**) calculated from time of first sniff. See also **Extended Data Fig. 4d**.

(**k**) Correlation between time-to-peak of the X_1 integration dimension and latency from first sniff to the first attack (linear regression, R^2 = 0.978, ****p < 0.0001). Individual mice are color-coded.

(**l**) Schematic summary of results in (**j-k**) and **Extended Data Fig. 4b-f**.

(**m**) BTA of X_1 dimension aligned to the offset of the final attack bout. Dashed lines: exponential curve-fit of mean activity.

(**n**) Area under the curves (AUC) in (**m**) for 100s after the last attack offset.

(**o**) Time constants of rSLDS dimensions.

(**p**) Dynamics of individual X_1-weighted neurons. (**p$_i$**) Stem plot of individual cell weights from 18-hr fasted mice; red circles, weights >2SD; (**p$_{ii}$**) Activity of X_1-weighted neurons in fed (left) vs. 18-hr fasted (right) condition; (**p$_{iii}$**) Representative traces of neurons from (**p$_{ii}$**), aligned to the first sniffing bout.

(**q**) ECDF of average autocorrelation half-widths (ACHWs) for X_1-weighted neurons' activity during male-male interactions (n=6 mice). See also **Extended Data Fig. 3g-j**.

(**r-s**) Representative flow fields of rSLDS models in (**f-g**) with neural trajectories color-coded by time (**r$_i$, s$_i$**) or behaviors (**r$_{ii}$, s$_{ii}$**) in both fed (**r**) and 18-hr fasted (**s**) states.

*p<0.05, **p*<0.01, ***p<0.001. For all figure panels, data are mean ± SEM (n=6 mice). See also **Extended Data Fig. 2, 3 and 4**.

Fig. 3 Prolonged fasting duration reveals biphasic effects on aggression and stability of VMHvl^Esr1 attractor dynamics.

Fig. 3 | Prolonged fasting duration reveals biphasic effects on aggression and stability of VMHvl^{Esr1} attractor dynamics.

(**a**) Schematic of prolonged fasting and its effects on resident-intruder assay.

(**b, c**) Quantification of aggression parameters: (**b**) time spent in attack (%) and (**c**) time spent in sniff (%) across various fasting durations in mice with miniscope. See also **Extended Data Fig. 1d, f and 2a**.

(**d**) rSLDS model performance as cvR^2 for 40-hr fasted conditions.

(**e**) Activity of rSLDS latent dimensions aligned with behaviors in a representative 40-hr fasted mouse. Burgundy and gray curves indicate the X_1 and X_2 dimensions, respectively.

(**f**) BTA of rSLDS dimensions (X_1-burgundy, X_2-gray) aligned to the first sniffing bout in the 18-hr fasted or 40-hr fasted states across mice (n = 6 or 5 mice). **f$_i$**: Replication of **Fig. 2i** for purposes of comparison.

(**g, h**) X_1 dynamics and activity in 40 hr-fasted mice. (**g**) BTA of X_1 dimension aligned to the first sniffing bout in 18-hr (blue) vs. 40-hr (purple) fasted states; (**h**) AUC in (**g**) for 100s after first sniffing onset.

(**i**) Time constants of rSLDS dimensions across various fasting conditions. i-inset: enlarged time constants in 40-hr fasted condition.

(**j**) Comparison of time constants of X_1 dimension (**j$_i$**) or ratio of time constants from the X_1 and X_2 dimensions (**j$_{ii}$**) across fasting conditions.

(**k**) ECDF of ACHWs from X_1-weighted neurons' activity during male-male interactions across fasting conditions.

(**l**) Representative flow field of rSLDS models (**l$_i$)** in (**e**) with neural trajectories color-coded by time (**l$_{ii}$**) or behaviors (**l$_{iii}$**) in a 40-hr fasted state.

(**m**) Schematic summary of results in (**b-l**) illustrating the biphasic effect of varying food deprivation levels on the aggressiveness and stability of VMHvl^{Esr1} population dynamics.

*$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$; ns, not significant. For all figure panels, data are mean ± SEM (n = 5 or 6 mice).

Fig. 4 Acute, titrated activation of ARC^AgRP neurons phenocopies biphasic starvation-induced shifts in aggression-encoding VMH^Esr1 attractor dynamics

Activation of hunger-encoding ARC^AgRP neurons recapitulates the effects of fasting on aggressive behavior

Activation of hunger-encoding ARC^AgRP neurons mimics the effects of fasting on attractor dynamics

Graded activation of ARC^AgRP neurons

Naturalistic food deprivation

Hunger exerts a flexible, biphasic modulation of aggression levels & attractor stability

Fig. 4 | Acute, titrated activation of ARC^{AgRP} neurons phenocopies biphasic starvation-induced shifts in aggression-encoding VMH^{Esr1} attractor dynamics.

(**a**) (left) Representative histological section showing hM3Dq-mCherry expression in ARC^{AgRP} neurons and cFos (yellow) induction after 1 mg/kg of DCZ treatment. (right) Schematic of activation of ARC^{AgRP} neurons by systemic DCZ doses, 40-50 min before male-male interaction in *ad libitum*-fed states.

(**b-d**) Quantification of aggression parameters: (**b**) latency to the first attack, (**c**) time spent attacking (%) and (**d**) latency to the first feeding bout during titrated chemogenetic activation of ARC^{AgRP} neurons.

(**e**) Titrated chemogenetic activation of ARC^{AgRP} neurons with miniscope imaging of VMHvl^{Esr1} neuronal activity. FOV from a representative mouse.

(**f**) VMHvl^{Esr1} activity raster (lower, heat map) and resident behavior (upper, raster) from a representative 0.5 mg/kg (left) or 1mg/kg DCZ-treated (right) mouse, aligned to intruder entry. "0.5mg/kg" and "1mg/kg" above the baseline raster indicate pre-trial treatment (see (**a**)).

(**g**) rSLDS model performance as cvR^2 for 0, 0.5, 1.0 mg/kg DCZ conditions (n = 3 mice).

(**h-j**) X$_1$ dynamics with graded ARC^{AgRP} activation. (**h**) BTA of X$_1$ and X$_2$ dimensions, (**i**) Time constants of X$_1$ dimension, and (**j**) ECDF of ACHWs of X$_1$-weighted neurons under three different DCZ doses.

(**k-m**) Effects of starvation. (**k**) BTA of X$_1$ and X$_2$ dimensions, (**l**) Time constants of X$_1$ dimensions, and (**m**) EDF of ACHWs of X$_1$-weighted neurons under naturalistic food deprivation conditions. Data reproduced from **Fig. 2h, i; 3f, j and k** to facilitate comparison with (**h-j**).

(**n**) Schematic illustrating biphasic modulation of aggression and stability of the attractor as a function of levels of food deprivation or artificially induced hunger.

*$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$; ns, not significant. For all figure panels, data are mean ± SEM. See also **Extended Data Figures 5 and 6**.

Fig. 5 Persistent aggressiveness during intermittent fighting and feeding in hangry mice

Fig. 5 | Persistent aggressiveness during intermittent fighting and feeding in hangry mice.

(**a**) Schematic illustrating experimental design.

(**b**) Latency to the first eating bout upon the presentation of a chow pellet in fed vs. 18-hr fasted states.

(**c-d**) Probability of attack (upper) and eating behavior (lower) aligned with first food sniff onset in fed (**c**) and 18-hr fasted states (**d**-left), and aligned with the offset of first food sniff (**d**-right) (n=12 mice).

(**e**) Time spent in eating and attack behaviors during the simultaneous presence of a male and food in fed vs. 18-hr fasted states.

(**f**) Rasters of hierarchically clustered VMHvl^{Esr1} neuron activity (lower, heat map) with a behavior raster (upper) from a representative 8-hr fasted mouse.

(**g**) Representative traces of activity from male-behavior or eating-tuned neurons in (**f**). Colored vertical bars indicate behavior raster.

(**h**) Choice probability for male-directed behavior- vs. eating behavior-tuned cells (upper) and pie chart showing proportion of tuned cells (lower) (n=6 mice).

(**i**) Quantification of cvR^2 for GLM with male or food-related behaviors only vs. behaviors with a cell-coupling term from neural activity (n = 6 mice). See also **Extended Data Fig. 7c**.

(**j**) (lower) First three dimensions of an rSLDS model (X_1-X_3) from a representative mouse, aligned to male entry; (upper) behavior rasters.

(**k**) BTA of rSLDS dimensions X_1 (burgundy), X_2 (gray), and X_3 (green) dimensions aligned to the first sniff bout (n = 6 mice).

(**l**) BTAs of baseline-subtracted, normalized activity of X_1 and X_2 (upper row) and X_3 (lower row) aligned to (**l$_i$**) first attack, (**l$_{ii}$**) first eating bout, (**l$_{iii}$**) eating offset, and (**l$_{iv}$**) re-attack.

(**m**) Quantification of BTAs in X_1–X_3 dimensions during the four epochs in (**l**). One-way ANOVA with paired post-hoc tests with multiple comparison correction.

(**n**) Empirically measured decay constants of X_1 vs. X_3 activity following eating offset (**l$_{iii}$**).

(**o**) Accuracy of decoding eating vs. attack bouts using X_1 dimension activity (data) is not significantly better than shuffled control, reflecting similar level of X_1 activity during both behaviors (**l$_{i,ii}$**) (n = 6 mice).

(**p-r**) Schematics summarizing design (**p**) and results (**q, r**) from behavioral choice assay.

(**q**) Summary of activity in X_1 (left) vs. X_3 (right) dimensions during attack vs. eating. (**r**) Neural state-space trajectories of activity in rSLDS latent dimensions during periods of attacking vs. eating.

*p<0.05, **p<0.01, ****p<0.0001; ns, not significant. For all figure panels, data are mean ± SEM. See also **Extended Data Figures 7 and 8**.

Extended Data Fig. 1 | Additional information for Fig. 1

Hunger states modulate innate social behaviors during male-male or male-female interactions

Resident: ad-libitum fed vs 8hr fasted

a resident: C57B6/N
ad-libitum fed vs 8hrs fasted

Bi-phasic modulation of aggression by variable fasting duration

Sexual behaviors during male-female interaction under fed vs. 18 hr fasted states

g resident-intruder (RI) assay

Extended Data Fig. 1 | Hunger states modulate innate social behaviors during male-
male or male-female interactions; additional information for Fig. 1.

(a-c) (**a**) Schematic and quantifications of behaviors in fed vs. 8-hour fasted male
residents. (**b**) Time spent in attack or sniffing the male intruder (%), and (**c**) latency to the
first attack. These males underwent the same conditions as described in Fig. 1, except
for 8 hours of food deprivation instead of overnight fasting, with food removal beginning
at 9 AM (see Methods for more information, n = 8 mice).
1299
1300 **(d-f)** Quantification of aggression parameters across *ad libitum*-fed, 18-hr or 40-hr fasted
1301 states: (**d**) time spent in attack (%); (**e**) latency to the first attack from the first sniff; (**f**) time
1302 spent in sniffing (%). (n = 10 mice).
1303
(g-m) (**g**) Sexual behaviors of resident males during interactions with female intruders in
ad libitum-fed vs 18-hr fasted states; (**h**) quantifications of time spent sniffing females and
female-directed mounting or intromission (%). Inset: 22% of males in the fasted state
attacked female intruders; (**i**) average bout duration; (**j**) number of bouts per minute; (**k**)
Inter-bout interval; (**l**) latency to the first female-directed mounting, and (**m**) distribution
showing the percentage of mice engaging in sexual behaviors for the latency to the first
female-directed mounting in fed vs. fasted conditions. For (i), one outlier data point with
parentheses, since the difference remained statistically significant even with its exclusion.
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1313 *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p< 0.0001$; ns, not significant. For all figure panels,
1314 data are mean ± SEM.
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Extended Data Fig. 2 | Additional information for Fig. 2.

Aggressive behaviors and tuning properties of VMHvl^Esr1 neurons across *ad-libitum* fed vs. 18 hr fasted states

Aggressive behaviors in male resident with microendoscope imaging in fed vs. 18hr fasted states (See Fig. 2)

Bulk VMHvl^Esr1 neural activity levels in fed vs. 18hr fasted states

Male-directed behavior tuning properties of VMHvl^Esr1 neurons in fed vs. 18hr fasted states

Bulk neural activity levels of *attack-tuned cells* in fed vs. 18hr fasted states

Bulk neural activity levels of *sniffing-tuned cells* in fed vs. 18hr fasted states

Extended Data Fig. 2 | Aggressive behaviors and tuning properties of VMHvl^{Esr1}
neurons in *ad-libitum* fed vs. 18-hr fasted states; additional information for Fig. 2.

(a-e) Quantification of aggression parameters for mice shown in Fig. 2: (**a**) time spent
sniffing the male intruder (%); (**b**) time spent in attack (%); (**c**) average attack bout
duration; (**d**) Inter-bout interval of attack; (**e**) time from male entry to first sniff and from
first sniff to the first attack. **e$_{ii}$**: an expanded panel for **e$_i$**-box. (n = 6 mice).
1334
1335 (**f**) (left) BTA of bulk VMHvl^{Esr1} activity aligned to the onset of first sniffing showing no
1336 significant difference between *ad-libitum* fed and 18-hr fasted states (n = 6 mice). (right)
1337 Dashed lines for individual mice.
1338
1339 (**g-h**) (**g**) Average neuronal activity for baseline and 1 min following the first sniff; (**h**)
1340 Average baseline subtracted z-score activity between fed vs. 18-hr fasted conditions (ns,
1341 $p > 0.05$).
1342
1343 (**i**) Time to peak z-score following first sniffing (ns, $p > 0.05$, paired t-test).
1344
1345 (**j**) BTA of bulk VMHvl^{Esr1} activity aligned to the onset of the first attack for between fed vs.
1346 fasted states (ns, $p > 0.05$).
1347
1348 (**k-l**) Choice probability for male-directed sniffing vs. attack behavior and percentage of
1349 cells with tuning preference in (**k**) fed and (**l**) fasted states.
1350
1351 (**m, q**) Fraction of neurons for attack-tuned (left) and sniff-tuned (right) across fed (**m**) and
1352 fasted (**q**) states.
1353
1354 (**n, r**) BTA of VMHvl^{Esr1} neuronal population tuned to attack vs. sniffing from the choice
1355 probability analysis, aligned to the onset of first sniffing between *ad-libitum* fed and 18-hr
1356 fasted states (n = 6 mice).
1357
1358 *$p<0.05$; ns, not significant. For all figure panels, data are mean ± SEM.

Extended Data Fig. 3 | Additional information for Fig. 2

Improved GLM fits with cell coupling and enhanced persistence of VMHvl^Esr1 neurons in fasted mice

Gerneralized Linear encoding Model with behavior or behavior+cell coupling regressor

a Inputs

generalized linear model

① male-directed behaviors
sniff
attack

behavior only

b only with behaviors

fed (n=6 mice)

mean cvR²=0.151

18hrs fasted (n=6 mice)

mean cvR²=0.168

fraction of variance explained by GLM (cvR²)

c Inputs

generalized linear model

① male-directed behaviors
sniff
attack

② cell-coupling +temporal history

n_1
n_{n-1}
time

regression filters

d behaviors +cell-coupling

fed (n=6 mice)

mean cvR²=0.479

18hrs fasted (n=6 mice)

mean cvR²=0.403

fraction of variance explained by GLM (cvR²)

e only with behaviors / behaviors +cell-coupling

variance explained by GLM (cvR²)

0.5

ad-lib fed
18hrs fasted

f only with behaviors / behaviors+cell-coupling

variance explained by GLM (cvR²)

**** **

ad-lib fed
18hrs fasted

Persistence of VMHvl^Esr1 neural activity with GCaMP8m

g example mouse

1st sniff

z-scored activity

n_{46}
n_{54}
n_{58}
n_{59}

2σ
20s
fasted — fed

h ramping persistent cell

1st sniff

z-scored activity

2σ
0   50   100   150
time (s)

i autocorrelation half-width (s)

1
0.5

ACHW

1
0.5

1
0.5

autocorrelation

0   10   20   30   40
offset (seconds)

j decay dynamics of individual neurons

n=6 mice

****

% of cells (norm to 0-1)

1
0.5

0   50
ACHW from all neurons(s)

count   150   mean= 9.76s   fed
0   ACHW(s)   50

count   150   mean = 11.6s   fasted
0   ACHW(s)   50

Extended Data Fig. 3 | Improved GLM fits with cell coupling and enhanced persistence of VMHvl^{Esr1} neurons; additional information for Fig. 2.

(**a**) Schematics of a GLM to predict individual cell activity from a behavior regressor.

(**b**) Histogram with variance explained (cvR^2) across all neurons, n=6 mice from behavior-only GLM in the fed (above) and fasted (below) states. Solid line: mean; dashed line: median value.

(**c**) Schematics of GLM to predict individual cell activity from behavior and cell-cell coupling.

(**d**) Histogram with cvR^2 across all neurons, n=6 mice from behavior + cell-coupling GLM in fed (above) and fasted (below) states. Solid line: mean; dashed line: median value.
(**e-f**) Quantification of cvR^2 in GLM with behavior + cell-coupling compared to the behavior-only regressor.

(**g**) Individual neural traces between *ad-libitum* fed vs. fasted states, showing persistence during male-male interaction with the GCaMP8m indicator, blue: fasted, brown: fed state.

(**h-i**) Individual example neural traces with the most extended (upper, 20s), medium (middle, 10s), and shorter (lower, 5s) ACHW.

(**j**) Distribution of cells for ACHW in fed vs. 18-hr fasted state for 6 mice. Histogram of ACHW (inset). Paired or unpaired t-test,

**p<0.01, ***p<0.001, ****p <0.0001; ns, not significant. For all figure panels, data are mean ± SEM.

Enhanced ramping and stability of aggression-encoding VMHvl[Esr1] attractor dynamics in 18 hr fasted state

a Data-driven probabilistic state-space modeling

rSLDS state distributions & behaviors

rSLDS modeling

model parameters learned

dynamical equation

$$\frac{dx}{dt} = A_z x + Bu$$

x : rSLDS dim.

neural activity
model prediction

dimensionality reduction

rSLDS states

A_1 A_2

A_3

dynamics matrix

dynamical features

line attractor

sniffing
attack

escalating aggression

example mouse   fed   18hrs

rSLDS states ❶❷❸
sniff
attack

Shorter latency to attack and ramping of integration dimension in 18hr fasted state

b 1st sniff — fasted, fed; raw activity from X_1 dim.; time aligned to 1st sniff (s); n=6 mice

c 1st sniff — fasted, fed; ns; raw activity from X_2 dim.; time aligned to 1st sniff (s); n=6 mice

d ramping rate to the 1st attack of X_1 dimension (zscore/s); *; ad-lib fed / 18hrs fasted

e_i latency to the 1st attack from 1st sniff (s); *; ad-lib fed / 18hrs fasted

e_ii time to peak of X_1 dimension (s); *; ad-lib fed / 18hrs fasted

f mouse: m1 m2 m3 m4 m5 m6

$R^2=0.85$ $p^{**}=0.0092$; time to peak of X_1 dimension (s); latency to 1st attack from 1st sniff(s); ● fasted

$R^2=0.9861$ $p^{****}<0.0001$; ○ fed

g_i rSLDS dimensions X_1 X_2; time constant of rSDLS dimensions (s); $p^*=0.01$; ad-lib fed

g_ii ratio of time constant X_1/X_2 ($\log_2$); *; ad-lib fed / 18hrs fasted

h flow field with neural trajectory; time(s) 0–100; line attractor; X_2; X_1

neural trajectory with behaviors 18hrs; sniff bouts; attack bouts; line attractor; mouse6

Extended Data Fig. 4 | Enhanced ramping and stability of aggression-encoding VMHvl^{Esr1} attractor dynamics in 18-hr fasted state; additional information for Fig. 2.

(**a**) (left) Schematics of rSLDS modeling. (right) Discrete states of rSLDS model and behavior raster in **Fig. 2f, g** from fed and fasted states.

(**b-c**) BTA of non-normalized activity in the X_1 dimension (**b**) or X_2 dimension (**c**), aligned to the first attack in the fasted and fed conditions (n = 6 mice). Compare with **Fig. 2h, i**.

(**d**) Ramping rate of the X_1 dimension in **Fig. 2j$_{ii}$**.

(**e**) Quantifications of (**e$_i$**) latency to the first attack and (**e$_{ii}$**) time to peak activity in the integration dimension from the first sniff in fed vs. fasted states.

(**f**) Correlation between the time to peak integration dimension and the latency to the first attack in the fasted state (left, closed circles) and the fed state (right, closed circles). Individual mice are color-coded. $R^2 = 0.85$, **$p = 0.0092$ (left); $R^2 = 0.98$, ****$p < 0.0001$ (right). One data point with () in the right panel, as the statistical significance did not change even with its exclusion.

(**g**) Quantifications of the ratio between time constants from X_1 and X_2 dimensions between fed vs. 18-hr fasted.

(**h**) Another example of flow field of rSLDS model with neural trajectory in the fasted state.

*$p<0.05$, **$p<0.01$, ***$p<0.001$; ns, not significant. For all figure panels, data are mean ± SEM.

Acute, titrated activation of ARC^AgRP neurons shifts aggression-encoding VMH^Esr1 attractor dynamics

Activation of hunger-encoding ARC^AgRP neurons mimics the effects of fasting on attractor dynamics

Ramping dynamics of VMHvl^Esr1 neural population dynamics under control vs medium-dose activation

Stability of VMHvl^Esr1 neural population dynamics

Extended Data Fig. 5 | Acute, titrated activation of ARC^{AgRP} neurons shifts aggression-encoding VMH^{Esr1} attractor dynamics; additional information for Fig. 4.

(**a**) Representative traces of X_1 dimension at each dose for ARC^{AgRP} neuronal activation from a representative mouse with male-directed behavior raster.

(**b**) Representative traces of X_1 and X_2 dimensions in medium-dose conditions showing rapid ramping and persistent activity in the X_1 dimension with a color-coded raster of sniffing (blue) or attack (red) behaviors across mice.

(**c**) BTA of X_1 dimensions comparing saline (gray) vs medium-dose (pink) conditions, highlighting the accelerated ramping in the medium dose.

(**d**) Quantification of the ramping rate from (**c**).

(**e**) Individual traces of X_1 dimension at the medium level of activation with rapid ramping (**e$_i$**) and AUC calculated for 100s after the first sniff (**e$_{ii}$**).

(**f**) Correlation between the time to the peak of the X_1 dimension and the latency to the first attack from the first sniff bout.

(**g-h**) BTA of X_1 dimensions comparing medium vs. high-dose condition: (**g**) difference in persistence of the first dimension of rSLDS; (**h**) quantifications of AUC after the first sniff.

(**i**) Time constant from X_1 and X_2 dimensions across three different conditions of chemogenetic activation of ARC^{AgRP} neurons.

(**j**) Quantification of the ratio between the time constants of X_1 and X_2 dimensions.

(**k**) Histogram of ACHWs across control, medium, and high-dose conditions in **Fig. 4j**.

(**l-m**) Quantification of (**l**) time constant for the X_1 dimension or (**m**) ratio between time constants for X_1 and X_2 dimensions across naturalistic food deprivation or activation of ARC^{AgRP} neuronal activity to induce hunger drive.

*$p<0.05$, **$p<0.01$; ns, not significant. For all figure panels, data are mean ± SEM.

Extended Data Fig. 6 | Additional information for Fig. 4

Acute, titrated activation of ARC^{AgRP} neurons phenocopies biphasic starvation-induced shifts in aggression-encoding VMH^{Esr1} attractor dynamics

Extended Data Fig. 6 | Acute, titrated activation of ARC^{AgRP} neurons phenocopies biphasic starvation-induced shifts in aggression-encoding VMH^{Esr1} attractor dynamics; additional information for Fig. 4.

(**a-d**) Representative flow fields with trajectory colored by time (middle) or behaviors (right) from rSLDS-modeled attractor dynamics under naturalistic food deprivation conditions for 18-hr (**a**) or 40-hr (**c**) and chemogenetic activation of ARC^{AgRP} neuronal activity at medium (**b**) or high-dose conditions (**d**).

(**e**) Schematic summarizing the effects of various hunger levels on aggression and aggressiveness-encoding VMHvl^{Esr1} neural population dynamics.

Extended Data Fig. 7 | Additional information for Fig. 5

A competing action for food elicits orthogonal perturbations in the VMHvl^{Esr1} attractor dynamics, with distinct tuning properties

Distribution of behaviors under competing states with food

a time spent in each behavior with male+food (%)

3.5% eating 3.7% attack
fed: 73.7, 15.9

32.7% eating 3.4% attack
fasted: 53.6, 5.8

eating, attack, food sniff, male sniff, others

b 67% of tested mice

time to re-attack from 1st food sniff offset (s)

p=0.06

ad-lib fed
18hrs fasted

(N=12 mice)

Male or food-directed behavior tuning properties of VMHvl neurons

male-directed behaviors: male sniff, attack
food-directed behaviors: food sniff, eating

or

cell-coupling +temporal history

generalized linear model

regression filters

single-cell neural activity

c$_i$ GLM model only with behaviors — mean cvR^2=0.27

c$_{ii}$ beh.+cell-coupling — mean cvR^2=0.52

variance explained by GLM (cvR^2)

rSLDS modeling under competing aggressive and hunger states with presence of male and food

d rSLDS modeling

variance explained by rSLDS dimensions

**

2d, 3d
No. of rSLDS dimensions

e mouse 2 — ♂in, food, ♂out, ♂in, ♂out — sniffiM, attack, sniff food, eating — X_1, X_2, X_3 — time (s) 0–1500

f mouse 3 — ♂in, food, ♂out, ♂in, ♂out — sniffiM, attack, sniff food, eating — X_1, X_2, X_3 — time (s) 0–600

g normalized activity in X_1 (baseline substrated)

ns

attack, re-attack

h decoding accuracy (attack vs eating from X_3)

**

data, shuffle

Single cell analysis of rSLDS dimensions

i weights of individual neurons in each rSLDS dimensions

mouse 1

X_1 >2.5std
X_2 >2.5std
X_3 >2.5std

weights

neurons

X_1 contributing cells
X_2 contributing cells
X_3 contributing cells

z-score activity

2σ 100s

j *choice probability for male directed vs eating behaviors*

X_1 contributing cells — <0.25, >0.75 — cells (%) — choice probability
male beh.-tuned :73% eating-tuned :6.7% *X1*

X_2 contributing cells — <0.25, >0.75 — cells (%) — choice probability
male beh.-tuned :29.1% eating-tuned :12.5% *X2*

X_3 contributing cells — <0.25, >0.75 — cells (%) — choice probability
male beh.-tuned :16.7% eating-tuned :67% *X3*

n = 6 mice

Extended Data Fig. 7 | A competing action for food elicits orthogonal perturbations in the VMHvl^{Esr1} attractor dynamics, with distinct tuning properties; additional information for Fig. 5.

(**a**) Pie charts of distribution of behaviors when males and food are present together in the fed state (left) and fasted state (right).

(**b**) Quantification of time to re-attack from the first food sniff offset in the fasted state. 67% of tested mice exhibited re-attack after transitioning to eating behavior (right).

(**c**) Histogram of GLMs with male or food-related behaviors only (**c$_i$**) and behaviors with cell-to-cell coupling from the neural activity (**c$_{ii}$**) of the fasting condition. Solid lines: mean values; dashed lines: median values.

(**d**) Quantification of rSLDS model performance using two vs. three dimensions.

(**e-f**) Representative traces of rSLDS dimensions (upper, X_1; middle, X_2; below, X_3) for (**e**) another mouse and (**f**) the mouse shown in **Fig. 5 f, g**.

(**g**) (left) X1-X3 weights for each individual cell in the example mouse used in **Fig. 5j**. (right) Representative traces of single-cell activity from X_1, X_2, and X_3-weighted neurons.

(**h**) Choice-probability of male-directed behaviors (attack + sniff) vs. feeding (eating) in the fasted state in X_1, X_2, X_3-weighted neurons (n = 6 mice).

(**i**) Quantification of X_1 activity after attack or re-attack, reused from **Fig. 5m$_i$ and 5m$_{iv}$**.

(**j**) Decoding accuracy distinguishing eating vs. attack bouts in real vs. shuffled data from the X_3 dimension (n = 6 mice). **$p<0.01$; ns, not significant. For all figure panels, data are mean ± SEM.

Extended Data Fig. 8 | Additional information for Fig. 5

Trajectories in rSLDS state space reveal distinct manifolds, with a persistent and attractive aggressive state under drive for feeding in the VMHvl^{Esr1} neural population

1586 **Extended Data Fig. 8 | Trajectories in rSLDS state space reveal distinct manifolds,**
1587 **with a persistent and attractive aggressive state under drive for feeding in the**
1588 **VMHvl^{Esr1} neural population; additional information for Fig. 5.**
1589

1590 (**a-c**) rSLDS modeling based on the state space of the X_1-X_2 dimensions with trajectories
1591 (**a**) colored by time, (**b**) by behavior, and (**c**) trajectories during attack and eating behavior
1592 bouts.

1593

1594 (**d**) Quantification of Euclidean distance in **Fig. 8c** from the line attractor for attack and
1595 eating behavior bouts.

1596

1597 (**e-g**) Neural state space of the X_1-X_3 dimensions with trajectories: (**e**) colored by time, (**f**)
1598 colored by behavior; (**g**) only trajectories during attack and eating.

1599

1600 (**h**) Quantification of Euclidean distance in **Fig. 8g** from the line attractor during attack
1601 and eating behavior bouts. **$p<0.01$; ns, not significant.

1602

1603 For all figure panels, data are mean ± SEM.