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Arc Regulates a "Second-Guessing" Cognitive Bias During Naturalistic Foraging

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SUMMARY

Foraging involves innate decision heuristics that are adapted for the wild but can cause economically irrational cognitive biases in some contexts. The mechanisms underlying cognitive biases are poorly understood but likely involve genetic mechanisms. Here, we investigate foraging in fasted mice using a naturalistic paradigm and uncover an innate “second-guessing” cognitive bias that involves repeatedly investigating a former depleted food patch instead of consuming available food. Second-guessing is economically irrational because it incurs energetic costs in place of caloric benefits. Since learning and memory are involved, we tested roles for *Arc* and found that *Arc*$^{-/-}$ mice lack second-guessing, which causes increased food consumption in males during foraging. Using unsupervised machine learning, decompositions of *Arc*$^{-/-}$ and $^{+/+}$ mouse behavior show that *Arc* affects discrete foraging sequences involved in second-guessing and later stages of memory. Thus, revealing a genetic basis for this bias and ethological role for *Arc* in a naturalistic behavior.

INTRODUCTION

Studies of animal foraging and human psychology have helped to uncover important rules and mechanisms of cognition and decision making, giving rise to the fields of behavioral economics and neuroeconomics (Gigerenzer and Gaissmaier, 2011; Hayden, 2018; Kalenscher and Wingerden, 2011; Pearson et al., 2014; Tversky and Kahneman, 1974). These fields uncovered cognitive biases that are deviations from optimal economic decisions and can reveal innate heuristics that are "short-cut" rules the brain evolved for faster and more efficient decisions in the wild (Gigerenzer and Gaissmaier, 2011; Tversky and Kahneman, 1974). Mechanistic studies of decision making typically focus on defining neurophysiological correlates, neuronal circuits and mathematical models of decision processes (Daw et al., 2006; Dayan and Daw, 2008; Fetsch et al., 2012; Gold and Shadlen, 2007; Gomez-Marin and Mainen, 2016; Kepecs et al., 2008; Kiani and Shadlen, 2009; Lak et al., 2020; Masset et al., 2020; Matsumori et al., 2018; Meyniel et al., 2015). However, at least some cognitive biases are shared across different species (Hayden, 2018; Kalenscher and Wingerden, 2011; Mobbs et al., 2018), indicating evolutionarily conservation and a genetic basis. Indeed, given that evolutionarily conserved cognitive biases are economically irrational (by definition) and involve innate decision heuristics, they are components of behavior that are likely to be strongly genetically determined. So far however, little is known about the genetic basis of the different cognitive biases involved in foraging and economic decisions.

The discovery of genetically-controlled behavioral components that evolved in the wild faces difficulties due to the lack of precisely controlled paradigms that emulate natural conditions (Gomez-Marin and Ghazanfar, 2019). Most lab studies focus on simplified binary choice tests (Hayden and Walton, 2014). However, in nature, the *entire behavioral sequence* before, during, and after a choice shapes benefits and costs, which is subject to natural selection. Objective approaches to study more naturalistic behaviors have been lacking, yet the development of data-driven methods to decompose

spontaneous behaviors into discrete components is a growing area (Datta et al., 2019; Krakauer et al., 2017). We recently developed a naturalistic foraging assay and unsupervised machine learning methods for top-down decompositions of foraging in mice, revealing the structure and genetic mechanisms that affect different behavior components (Bonthuis et al., 2022; Hörndli et al., 2019). Our paradigm mimics key elements of the wild context, including a freely accessible home, sand patches of potential food, seeds, and digging. With this approach, we found that foraging is constructed from finite, genetically controlled behavioral sequences that we call “modules” (Hörndli et al., 2019). Foraging modules are reproducible decision and action sequences expressed during round trips from the home that can range from less than a second to hundreds of seconds in duration. We are now poised to investigate genetic mechanisms underlying different components of naturalistic foraging.

Here, we deeply analyze foraging in fasted mice and uncover a cognitive bias that involves repeatedly investigating a former and depleted food patch rather than consuming readily available food. We refer to this as “second-guessing” because it appears to involve repeatedly checking a learned former food patch even after learning it doesn’t contain food. Second-guessing behavior is an irrational cognitive bias that occurs in naïve male and female mice, suggesting a genetically determined decision heuristic. Given that memory confidence and repeated checks on memory accuracy have important roles in doubt and repetitive behaviors (Hout and Kindt, 2003; Olson et al., 2016; Radomsky et al., 2014), we hypothesized that second-guessing is linked to memory and tested roles for the synaptic plasticity and memory gene, *Activity-regulated cytoskeletal associated protein* (*Arc*) (Link et al., 1995; Lyford et al., 1995). *Arc* is critical for long-term forms of synaptic plasticity and memory (Shepherd and Bear, 2011). Studies using standardized lab behavior tests, such as spatial memory (Plath et al., 2006; Vazdarjanova et al., 2006; Wall et al., 2018), fear conditioning (Nakayama et al., 2016; Plath et al., 2006; Ploski et al., 2008) and behavioral responses to novelty and stress

(Guzowski et al., 1999; Montag-Sallaz et al., 1999; Penrod et al., 2019) found that *Arc* is required for memory consolidation. However, roles for *Arc* in naturalistic foraging have not been tested. We show that initial learning and memory responses with a 24hr delay between exploration and foraging are grossly intact in *Arc*$^{-/-}$ mice, but they show complete loss of second-guessing behavior that is replaced with increased food consumption in males. Using machine learning decompositions of the behavior, we uncover a finite set of *Arc*-controlled foraging modules that underlie second-guessing versus feeding decisions. Thus, our study reveals a genetically controlled “second-guessing” cognitive bias in mice, links specific foraging modules to this cognitive bias and reveals unique ethological roles for *Arc* in foraging and memory responses.

RESULTS

Identification of a "Second-Guessing" Cognitive Bias in Fasted, Foraging Mice

To investigate the nature of different memory responses during foraging, we designed a naturalistic paradigm in which mice have spontaneous access to a foraging arena and their home. Using methods from the foraging ecology field, our arena includes patches of sand and one has seeds. Mice learn the location of a food patch in the foraging arena during an Exploration phase (**Fig. 1A**) and then 24hrs later, the mice are provided with access to the arena again during a Foraging phase, but the food is now in a different location (Pot4) (**Fig. 1B**). Thus, we can test whether the mice express a memory response to the former food patch (Pot2) by measuring the time spent at Pot2 relative to patches that do not contain food (Pots 1 and 3). We also learn whether the mice discover and exploit the novel food patch (Pot4) by analyzing time spent at this location (**Fig. 1B**), and ultimately, decompose the behavior using unsupervised machine learning methods to uncover foraging modules (see below). Overall, this paradigm enables us to investigate how memory of a former food patch and environment can shape foraging behaviors and decisions.

We performed this foraging test on a cohort of wild-type adult male and female mice on a C57BL/6J background and first characterized interactions with the former food patch, Pot2, in the Foraging phase of the task. By analyzing the average time spent at Pot2 in time bins over the 30-minute testing period over all the mice, we found that males (**Fig. 1C, blue**) and females (**Fig. 1C, Pot2, pink**) show 2 major peaks of interaction with the former food patch (**Fig. 1C, stars**). The first peak shows the most Pot2 interactions over the trial, reaching a peak at ~3 min in males and ~4 min in females. This first stage of interaction then wanes, reaching a minimum interaction time at ~10 min in males and 9 min in females (**Fig. 1C, blue and pink lollypops**), which is then followed by a second stage increase that peaks at ~12 min in males and 13 min in females (**Fig. 1C, blue and pink**

stars). This second stage of increased interaction wanes by 16 min in males and 17 min in females (**Fig. 1C, blue and pink lollypops**), and is followed by a third stage of reduced, but ongoing interactions with Pot2 until the end of the 30 min assay. From these major peaks and valleys in the data, we defined 3 stages of interaction with the former food patch (Pot 2): (1) Stage 1, 0-9 min; (2) Stage 2, 9-16 min; and (3) Stage 3, 16-30 min (**Fig. 1C, top purple lines**). In contrast to interactions with Pot2, interactions with the new food patch, Pot4, do not separate into similar stages, but increase steadily and reach a peak at ~16 min that persists until the end of the assay (**Fig. 1C, Pot4**). Overall, our results indicate 3 stages of interaction with the former food patch that appear to reflect discrete waves of memory response behaviors.

We further determined that the Pot2 interactions involve discrete stages of memory response by comparing the time spent at Pot2 to that for Pot1, which is a control patch that never contained food in the Exploration phase and is not close to the new food patch (Pot4) in the Foraging phase. Our results show significantly increased average and cumulative time at Pot2 compared to Pot1 during Stages 1 and 2, but not 3 (**Fig. 1D, top plot shows mean time; lower plots show cumulative time by stage**). Moreover, in males, interactions with Pot2 drop to levels that nearly match Pot1 interactions and delineate the Stage 2 memory response boundaries (**Fig. 1D, purple lines, top plot)**. Similar, albeit expanded Stage 2 response boundaries are also visible in females **(Fig. 1E, purple lines)**, and female cumulative interaction results also show significantly increased Pot2 compared to Pot1 interactions in Stages 1 and 2, but not 3 (**Fig. 1E, lower plots**). Thus, our findings show that Stages 1 and 2 are two significant and distinct waves of memory response behavior in which mice show increased interactions with a previously learned, former food patch.

In Stage 1, the animal's increased interaction with the former food patch is rational given the initial expectation of food in this location. However, the Stage 2 increase in interactions with Pot2 is an economically irrational decision because the animal is fasted and knows that food is not located there, but is abundant in Pot4. All mice have visited Pot4 by ~2 minutes after entering the arena during the Foraging phase, with a mean latency of 25 seconds. We tested the possibility that mice perform this Stage 2 behavior because they have consumed all the food in Pot4 and are now looking for more. However, we found that these fasted mice consume <20% of the total food available during each phase, showing that they do not express this behavior because they have run out of food in Pot4 (**Fig. 1F**). It is also not the case that the mice are failing to find the food in Pot4. We observed that they rapidly discover and show significantly increased interactions with the Pot4 food patch within the first minutes of the assay (**Fig. 1G and H**). Collectively, our results show that the Stage 2 behavior is a discrete memory response during foraging that is directed at a former food patch that no longer contains food. Given the energetic costs versus caloric benefits for a fasted mouse, the Stage 2 memory response is suggestive of an economically irrational cognitive bias to repeatedly "second guess" a former food patch. We therefore refer to this behavior in Stage 2 as "second-guessing".

Second-guessing behavior could be affected by memory consolidation and the duration of the time separating the Exploration and Foraging phases of our assay. Here, we tested whether the duration of the consolidation period significantly affects second guessing by comparing a 4 hr (shorter-term memory) versus 24hr (longer-term memory) separation between the two phases. We found that the cumulative time at Pot2 over the total assay and during the Stage 2 second-guessing behavior are not significantly different between the 4hr and 24hr conditions (**Fig. 1I and J**). Therefore, second guessing is not significantly affected by these shorter versus longer periods of memory

consolidation. We next tested if “second-guessing” is a genetically determined cognitive bias during foraging.

Arc Knockout Mice Show Selective Loss of Second-Guessing with an Associated Increase in Food Consumption in Males

Arc is a logical initial gene candidate for affecting second-guessing behavior and memory responses. It is considered a master regulator of synaptic plasticity and long-term memory consolidation (Shepherd and Bear, 2011). However, roles for *Arc* in naturalistic foraging have not been studied indicating an opportunity to uncover its functions in this ethologically important context. Here, we profiled foraging in *Arc*$^{-/-}$ mice compared to $^{+/+}$ littermate controls in our assay. First, we tested how *Arc*$^{-/-}$ mice learn during the Exploration phase by examining how they adapt their behavior in the Foraging phase assay 24hrs later (**Fig. 2A**). We found that <u>both</u> *Arc*$^{-/-}$ and $^{+/+}$ mice show a significantly reduced latency to enter the foraging arena during the Foraging phase compared to the Exploration phase (**Fig. 2B**). This shows that the $^{-/-}$ mice recall the general environment and adapt their behavior accordingly. We further found that both male and female *Arc*$^{-/-}$ and $^{+/+}$ mice show a significant preference for Pot2 within the first 5 minutes of the Foraging phase, indicating an initial memory response to the former food patch (**Fig. 2C and D**). Therefore, *Arc*$^{-/-}$ mice forage, learn the location of the food in the Exploration phase and show initial memory response behaviors 24hrs after Exploration.

By analyzing plots of the cumulative time spent at Pot2 over course of the assay, we found a significant genotype difference in which $^{+/+}$ males and females continue to accumulate increased time at Pot2, but $^{-/-}$ mice exhibit a significant reduction in Pot2 interactions that becomes pronounced after approximately 8 minutes into the assay in males (**Fig. 2E**) and 15 minutes in females (**Fig. 2F**). This

finding shows that *Arc* most strongly affects later stage, rather than initial memory responses to the former food patch, Pot2.

The apparent late-stage memory response phenotype could be secondary to changes to the motivation to feed in *Arc*$^{-/-}$ mice. To test this, we examined food consumption during the Exploration phase, which lacks a memory response component, and found that *Arc*$^{-/-}$ mice do not consume less food or spend less time at the food (**Fig. S1A and B**). This indicates that their drive to feed is not significantly reduced compared to $^{+/+}$ mice in the assay. Alternatively, *Arc*$^{-/-}$ mice might be slow to discover the novel food patch in the Foraging phase and therefore express a delayed, but elevated interest in Pot4 over Pot2. However, we found that *Arc*$^{-/-}$ mice discover and significantly increase Pot4 interactions within the first ~8 minutes of the Foraging phase like $^{+/+}$ mice (**Fig. S1C**). Given that *Arc*$^{-/-}$ mice do not display overt reductions to the drive to consume or find food, we concluded that they display bona fide changes to later stage memory responses during foraging, rather motivations to feed. We therefore directly tested second-guessing.

To examine roles for *Arc* in second-guessing, we visualized the pattern of interactions with Pot2 over the course of the 30 min Foraging phase in 1 minute time bins, thereby revealing the Stage 1, 2 and 3 memory responses (**Fig. 3A and B**). We found that *Arc*$^{-/-}$ males show a specific loss of the Stage 2 second guessing behavior, as they no longer show a second wave of interest in Pot2 (**Fig. 3A**). Similar, albeit less robust effects were observed in females (**Fig. 3B**). We further tested this difference by computing the cumulative time at Pot2 during Stages 1, 2 and 3 in the *Arc*$^{-/-}$ versus $^{+/+}$ mice. We found that a significant main effect of the genotype ($^{-/-}$ versus $^{+/+}$) was observed – *Arc*$^{-/-}$ mice show a loss of Pot2 interactions for Stage 2, but not Stages 1 or 3 (**Fig. 3A, B;** see statistical results in top boxes). Thus, *Arc*$^{-/-}$ mice show selective loss of second-guessing during Foraging.

Given the absence of the Stage 2 second guessing response, we determined what the *Arc*$^{-/-}$ mice are doing in place of this behavior. We found that male KO mice show significantly increased food consumption in the Foraging phase (**Fig. 3E**) and shift to significantly increased interactions with the Pot 4 food patch during the Stage 2 memory response (**Fig. 3F**). This effect was not observed in females (**Fig. 3E and G**) and deeper analyses of the females found that they did not spend significantly increased time at Pots 1 or 3 or in the home, indicating that *Arc*$^{-/-}$ females appear to redistribute their behavioral activity broadly during Stage 2 rather than focusing on a new site in the arena. Overall, we uncovered a specific role for *Arc* in second-guessing during foraging, and in the absence of the second-guessing bias *Arc*$^{-/-}$ males show more economically rational behavior by increasing food consumption.

Arc Controls a Discrete Set of Foraging Modules that Determine Second-Guessing

Previously, we found that foraging in mice is modular and constructed from finite, genetically controlled behavioral sequences (Hörndli et al., 2019). Here, we tested whether the second-guessing bias involves finite, genetically controlled modules of behavior that are specifically affected by *Arc*. To first uncover all the modules expressed by the cohort of *Arc*$^{-/-}$ and $^{+/+}$ mice, we applied our previously published DeepFeats algorithm to the foraging profiles of all mice (n=60) (Bonthuis et al., 2015; Hörndli et al., 2019). For each of the 1,609 round trip foraging excursions expressed by the mice, we captured hundreds of measures of how the mice move and where they go while foraging. Principal component analysis (PCA) was applied for data dimension reduction in combination with the DeepFeats behavioral module detection algorithm. Our analysis found that 8 principal components best reveal candidate modules in our training dataset partition (**Fig. S2A,B**). We found 43 clusters of different foraging sequences that reflect candidate foraging modules (**Fig S2C**). To test whether any

of these clusters are bona fide, reproducible modules, we performed a modified in-group proportion permutation test to evaluate training data cluster reproducibility in a test dataset partition (**Fig. S2C,D**). We found that 24 of the 43 clusters are significantly reproduced in the test set and these were therefore defined as significant foraging modules (**Fig. S2D**). The results revealed that 942 of the 1,609 total round trip foraging excursions reflect modules, while the remaining are more stochastic, non-modular behavioral sequences.

To test whether loss of *Arc* significantly affects foraging module expression patterns, we computed a transition matrix that captures the order of the module expression sequences expressed by all mice during the Exploration and Foraging phases. In our results, the y-axis of the transition matrix indicates each expressed module, the x-axis indicates the next module expressed in a sequence by the mouse, and the data in the matrix shows the relative number of times this transition from model "A" to module "B" occurred (**Fig. 4A,B**). A fisher's exact test of this data revealed that the expression of one module depends significantly on the identity of the previously expressed module in the Foraging phase for males (**Fig. 4A**), and in both phases for females (**Fig. 4B**). Thus, the module expression sequences are not random, but determined in these contexts, suggesting innate, genetically controlled behaviors. We compared module expression transitions between *Arc*$^{-/-}$ and $^{+/+}$ mice using a permutation test (see methods) and found that the sequential order of module expression differs significantly between *Arc*$^{-/-}$ and $^{+/+}$ males and females in the Foraging phase (**Fig. 4D, F**), but not the Exploration phase (**Fig. 4C, E**). This result shows that *Arc* significantly affects module expression during the phase of our task that involves prior learning of the environment.

Next, we tested whether *Arc*$^{-/-}$ mice show changes in the expression of specific modules linked to Stage 2 second-guessing in the Foraging phase. To begin, we tallied the expression frequency of

each module for the *Arc*$^{-/-}$ and $^{+/+}$ males and females for Stages 1, 2 and 3. We present the results in heatmaps that show modules with high versus low expression frequencies (**Fig. 4G-I**). Statistical analysis of the module expression data found differences between the $^{-/-}$ and $^{+/+}$ mice in Stages 2 and 3, but not Stage 1 (**Fig. 4G-I**). Further, the results revealed specific modules affected by loss of *Arc*, including foraging Module 1, which shows increased expression in *Arc*$^{-/-}$ mice in Stage 2 and 3, as well as Module 21, which shows decreased expression compared $^{+/+}$ littermate controls (**Fig. 4H and I**). Module 1 is a simple decision and action sequence that involves directly going from the home to the food patch (Pot4) and then returning to the home, while Module 21 is a complex sequence that involves interacting with the former food patch (Pot2), as well as other components of the environment (**Fig. 4H and I, insets**). The structure and decreased versus increased expression of Modules 21 and 1, respectively, reveals that these modules are primary behavioral mechanisms that underlie a switch from second guessing to food consumption in *Arc*$^{-/-}$ mice, especially males (see **Fig. 3E**). Our data further reveal that the preference to express Module 1 over Module 21 in *Arc*$^{-/-}$ mice arises during Stage 2 and persists during Stage 3 (**Fig. 4H and I**). A subset of other modules (Modules, 12, 6, 3,8) also contribute to significant differences in module expression between $^{-/-}$ and $^{+/+}$ mice during Stage 3, but not Stage 2, revealing important differences. Overall, we found that *Arc* regulates the expression of specific foraging modules that dictate second-guessing versus the decision to feed.

DISCUSSION

Cognitive biases are decisions and behaviors that are not economically optimal in a particular context, and their mechanistic basis is poorly understood. Our study uncovers a genetically controlled cognitive bias in fasted foraging mice that involves second-guessing a former food patch instead of consuming available food. We show that the second-guessing bias occurs in males and females, indicating an innate rather than learned response and the effect is strongest in males. *Arc*$^{-/-}$ males and female show loss of second-guessing and *Arc*$^{-/-}$ males display more economically rational behavior by increasing food consumption in the absence of second-guessing. We show that second-guessing is part of a stereotyped and modular foraging repertoire in mice that involves the expression of discrete foraging modules that are regulated by *Arc*. While *Arc*$^{-/-}$ mice lack second-guessing, their initial memory responses that reflect learning and recall of the foraging environment are grossly intact. Thus, our study reveals a specific role for *Arc* in regulating a second-guessing cognitive bias and later-stage memory responses during foraging of a previously explored environment. These findings set the stage for further work aimed at defining genetic mechanisms and behavioral modules for different cognitive biases.

Cognitive biases are thought to be caused by innate decision heuristics that evolved for efficient decision processes in an organisms' native environment (Group: et al., 2014). Such biases should therefore have a genetic basis. In support of this idea, we found that *Arc* is required for a second-guessing bias during foraging. Moreover, *Arc*$^{-/-}$ males show increased food consumption in place of second-guessing, which demonstrates that a cognitive bias can be modified to be more economically optimal by affecting the underlying genetic mechanisms. While second-guessing is an economically irrational behavior in our assay, it could have important adaptive advantages in the wild. For example, if food availability in patches is dynamic, such that food can appear, disappear and reappear quickly, then it may be important to have constantly updated knowledge of different food patches in the local

environment and the dynamics of food availability. Moreover, if animals must frequently abandon available food due to high risks of predation or encounters with conspecific competitors, then updated knowledge of alternative patches and frequent patch switching could be important for survival. Thus, it may make economic sense to repeatedly second-guess a depleted former food source to check for updates in food availability when a known food rich patch is available. More generally, our study shows that deep analyses of foraging in mice can uncover genetically determined cognitive biases. Since over 50 different cognitive biases have been described in humans (Baron, 2000; Croskerry, 2003), there are rich opportunities to test their conservation in mice and investigate the genetic mechanisms.

While both males and females display *Arc*-regulated second-guessing, the phenomenon is more robust in males. Moreover, unlike males, female *Arc*$^{-/-}$ mice do not consume more food in the absence of second-guessing, revealing a sex-difference in the alternative behavioral response. While sex differences in decision-making heuristics are debated (Croson and Gneezy, 2009; Mowrey and Portman, 2012), it is known that risk taking, impulsivity and behavioral prioritization differ between males and females that could affect the behavioral alternatives to second-guessing (Mowrey and Portman, 2012). Indeed, in our other studies important sex differences in foraging were observed in mice (Bonthuis et al., 2022; Hörndli et al., 2019). Here, at the level of foraging modules, both *Arc*$^{-/-}$ males and females show increased expression of Module 1 and decreased expression of Module 21, revealing shared behavioral effects at the module level. Module 1 involves a direct excursion from the home to the food patch and back, while Module 21 involves repeated visits to the former food patch (Pot2) and exploratory behavior. These results reveal the identity of discrete, *Arc*-controlled foraging modules that underlie second-guessing versus feeding. *Arc* is often considered a general regulator of synaptic plasticity and memory, and some lab tests suggest that *Arc*$^{-/-}$ mice fail to consolidate long-term memories (Guzowski et al., 2000; Plath et al., 2006; Ploski et al., 2008). However, our foraging results

show that initial Stage 1 memory responses are grossly intact in *Arc*$^{-/-}$ mice, while Stage 2 second guessing and later-stage memory responses are more strongly affected. This could be due to changes in cognitive flexibility and perseveration, which have been reported in *Arc* transgenic mice where disruption of Arc protein degradation led to abnormal synaptic plasticity and behavior (Wall et al., 2018). *Arc*$^{-/-}$ mice may also have changes to memory robustness that affect second-guessing. Overall, our foraging study indicates that *Arc*'s role in learning and memory are more task, context and sex-specific than has been appreciated. Future conditional genetic studies are needed to define the brain regions and neural circuits in which *Arc* regulates second-guessing in males and females.

We previously found that foraging patterns in mice are constructed from finite, genetically controlled modules (Bonthuis et al., 2022; Hörndli et al., 2019). Here, we uncovered evidence that specific foraging modules can underlie a cognitive bias. *Arc*$^{-/-}$ mice show significant changes to the sequential order of module expression in the Foraging phase of our task compared to *Arc*$^{+/+}$ mice. No effect on module expression order was observed in the naïve Exploration phase, indicating specific roles for *Arc* in affecting foraging in a learned environment. Our analysis of module expression in Stages 1, 2 and 3 during Foraging revealed that *Arc* regulates specific modules in Stages 2 and 3, with links to second-guessing versus feeding. We hypothesize that foraging modules reflect the effects of innate decision heuristics that drive efficient experience-dependent decision-making processes in the wild. Modularity enhances evolvability in biological systems, such that existing modules can be reorganized, duplicated and modified without recreating their constituent parts and structure *de novo* (Lorenz et al., 2011). While modularity is a component of all biological systems (Hartwell et al., 1999; Lorenz et al., 2011; Melo et al., 2016; Wagner et al., 2007), it is a relatively new concept in behavioral economics. Stereotyped, hierarchical and modular behavior has been described in *C. Elegans, Drosophila* and mice (Berridge, 1990; Eilam and Golani, 1989; Hörndli et al., 2019; Kafkafi et al., 2003; Wiltschko et

al., 2015). We expect that genetic mechanisms exist that control the form, timing and expression frequency of second-guessing related behavior modules (Modules 1 and 21). Our findings provide a rationale for expanded studies of the genetic mechanisms controlling innate decision heuristics, and cognitive biases, and how they interact with different internal states, such as fasting. Second-guessing could share mechanisms with doubt and obsessive-compulsive behaviors, making the dissection of the mechanisms involved of potential biomedical importance (Bang and Fleming, 2018; Radomsky et al., 2014).

LIMITATIONS OF THE STUDY

Our study used fasted mice to study the cognitive bias of investigating former food patches versus eating available food. We have not determined how different internal metabolic states affect second-guessing, which limits our understanding of when and how this bias arises. Moreover, our focus on fasted mice differs from published studies of *Arc*$^{-/-}$ mice that reported loss of long-term memory consolidation and may contribute to differences in which we observe that some initial memory responses are intact in *Arc*$^{-/-}$ mice. It is also possible that memory consolidation in this naturalistic foraging task may take longer than 24hrs and thus may only be Arc sensitive over longer periods between exploration and foraging.

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AUTHOR CONTRIBUTIONS

A.R. performed the behavioral experiments in the *Arc* knockout mice. C.S.H. performed the data analysis and made the figures. C.G. and J.D.S. wrote the manuscript with input from all authors, supervised the study design, methods and data interpretation and provided funding.

DECLARATION OF INTERESTS

C.G. is a co-founder of and has equity in Storyline Health Inc., which uses artificial intelligence to build scalable research and clinical tools for precision medicine, and has equity and/or advisory roles in Rubicon A.I., DepoIQ, Lantern and Uncharted Health.

STAR METHODS

RESOURCE AVAILABILITY

Lead Contact

- Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Christopher Gregg (chris.gregg@neuro.utah.edu).

Materials Availability

- Datasets generated in this study are available from the Gregg lab.

Data and Code Availability

- All datasets and original code are available from the lead contact upon request.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Mice

Housing and husbandry

All experiments were conducted in compliance with protocols approved by the University of Utah institutional animal care and use committee (IACUC). C57BL6/J and *Arc/Arg3.1* knockout mice were bred and housed on static racks in the Biopolymers Building near the lab's behavioral testing room on a 12hr reversed light, 11pm on and 11am off. The generation of the *Arc/Arg3.1* knockout mouse line has been previously described (Plath et al., 2006). All mice were given water and food (Harlan-Teklad 2920X soy protein-free) *ad libitum*, with the exception of a single overnight fast for mice tested for foraging behavior (see METHOD DETAILS, *Behavior*, foraging). Adult breeders (6 weeks to 1 year of age) were paired continuously, and pups were weaned at postnatal day 21 (P21) and cohoused with up to five same-sex littermates or similar aged same-sex mice of the same line; mice were never singly housed. Ear punches were taken at P21 for both genotyping biopsy samples and mouse identification purposes. Genotyping was performed by Transnetyx.

Genotyping

Ear punches taken at P7-P21 were lysed in 75µL of 25mM NaOH + 0.25mM EDTA with a 1 hour incubation in a thermalcycler at 98˚C. Lysates were then pH neutralized with an equal volume of 40mM Tris.HCl, pH5.5. Two µL of lysates were then added to make 20µL PCR reactions with DreamTaq Green Master Mix (ThermoFisher, Cat# K1081) and 0.5µM primers.

METHOD DETAILS

Foraging

Foraging behavior testing was performed as detailed previously (Hörndli et al., 2019). In brief, in preparation for the foraging assay, mice were first habituated with sand (Jurassic play sand, Jurassic Sand) and seeds (Whole millet, Living Whole Foods) for two days in their home cage. On day one, seeds are spread on top of sand in the bottom of a Petri dish and the dish is placed on the bedding in the home cage for the mice and pups to explore. On day two, seeds are covered with sand in the bottom of the Petri dish in the home cage for the mice and pups to dig in and explore. To motivate animals to feed, mice were food deprived prior to testing to achieve 8%–10% weight loss at the time of testing. We selected this weight loss target after several pilot studies with the goal of achieving some consistency in the motivational states of the animals at different ages and not compromising health or activity. To achieve the intended weight loss and motivational state, adult mice were food deprived for 24 hours. Water is available *ad libitum* at all times except when mice are in testing cage (2 × 1 hour).

Mice are housed in a room with an 11:00 – 23:00 dark cycle, so that testing is performed during the dark cycle. For testing, mice are moved into the behavior room prior to the start of testing for at least 1 hour for habituation to the new room. All testing is performed in the dark and video recording is done using infrared illumination and all manual procedures are done in the dark using red light. The mouse to be tested, and their home cage soiled bedding, are moved to the testing-cage and allowed to habituate. At the start of testing, the testing-cage is attached to the arena via the tunnel, the mouse now has access to the arena and video recording starts for the Exploration phase. Mouse behavior is recorded continuously during the 30 min Exploration phase trial under infrared lights. Noldus Ethovision software v14 were used for video tracking. After completing the Exploration phase, the mouse is returned to the testing cage with water but no food until the Foraging phase 24 hours later. For the Foraging phase, the testing cage is then gently attached to the tunnel and access to the arena is possible and the Foraging trial begins. Video recording of the Foraging phase is performed for 30 minutes. After testing, mice are placed in a new cage with food and are returned to the mouse colony room. Between each Exploration and Foraging phase trial, the entire arena, including walls, platform, tunnel and steel pots, are wiped clean with 70% ethanol.

Preparation of Sand and Seed Pots for the Foraging Assay

Three stainless steel pots (Resco, diameter 5.5cm, depth 4cm) were filled with 95 g of sand. For the Exploration phase, 1 pot is filled with 80 g of sand covered with 2.5g of seeds. On top of seeds, a layer of 12 g of sand is added to cover seeds. This sand is then covered with 0.5g of seeds. This pot is placed in position 2 in the arena. For the Foraging phase, 1 pot is filled with 80 g of sand, 3g of seeds on top of sand and additional 12 g of sand to cover all seeds. This pot is placed in position 4 in the arena. All pots are weighed before and after the trial to measure the sand displaced from each pot. Remaining seeds and hulls left in the pot and on the platform are measured after each Exploration or Foraging trial to determine the amount of seeds consumed by the mouse during the trial. Used sand is collected after every trial and set aside. At the completion of all testing, the used sand is autoclaved before reuse in future trials.

Foraging Arena Construction

The foraging arena, tunnel and testing cage were custom built with acrylic plastic (Delvies Plastics, Salt Lake City, UT, USA). The 14 cm long tunnel enters the platform from underneath through one of the five 5.5 cm diameter holes in the arena platform. The platform is 8 cm above stage level and is made from 0.5 cm thick white Plexiglas. The arena is made from a transparent Plexiglas tube and the 0.4 cm thick walls raise 42 cm above the platform. The arena has a diameter of 35 cm. The walls of the arena were roughened with sandpaper to limit glaring and recording artifacts.

Arena Tracking Zones

The arena is organized into zones that are used to breakdown the behavior and foraging strategies used by each animal in the assay. The arena is divided into five sectors and the boundary of each sector is the midpoint

between two pots. The arena is further divided into three concentric circles, including the middle center zone, the intermediate zone and the outer wall zone. The outer radius of the *Intermediate* zone intersects with the center of the pots and tunnel entry. The radius of the *Center* zone is half the radius of the *Intermediate* zone. A zone is also created around each pot in the arena. *Pot* zones have a radius of 1.7x the radius of the pot itself. Finally, to learn about the behavior of the animal related to entries to and exits from the arena, we define zones around the tunnel entry. The *Tunnel Entry* zone aligns with the entry hole of the actual tunnel. The *In Tunnel* zone is covering the most peripheral area of the *Tunnel Entry* and tracks the mouse just before leaving the arena completely. Whenever the mouse is in the cage, the tracking system is recording the mouse as being in the *In Tunnel* zone. The *Tunnel Zone* area has the same radius as the *Pot* zones.

Automated Tracking

At the start of the trial, the tracking begins with a 10 s delay to allow time for the connection of the testing-cage to the arena. The mouse is first tracked when it appears in the *In Tunnel zone* and position and movement is continuously recorded after this time point until the end of the 30 min Exploration or Foraging Phase. The XY position of the center of the mouse is video tracked with at a rate of 30 frames per second. For the data analysis, tracking data from 0-25 minutes are used. Time spent in each zone, latency to visit a zone and number of visits to each zone, as well as the distance traveled, are calculated using the Ethovision software. The data is exported as results for the total 25-minute trial duration, as well as in 5 minute time bins. Sand displacement and food consummation measures are collected and calculated manually.

Behavioral Measures

All measures captured during Exploration or Foraging phases of the assay are presented in (Stacher Hörndli et al., 2019). All ‘time spent in zone’, sand displaced, food consumed and zone visit measures were normalized to the total time spent in the arena (TTA) by dividing each value by TTA (x/TTA). For time bin values, the TTA for the corresponding time bin is used for normalization (i.e., x-1/TTA-1). All latencies to visit pots were normalized to the latency to enter the platform (LEP) by subtracting the LEP (x-LEP). Latency to the center zone after arena entry (LCAE) is already normalized to LEP and does not need any further normalization. All percentage measures do not need any normalization. Time on the platform itself and time in the tunnel (cage) are not included in the normalized dataset because they are closely related and redundant to TTA.

Locomotor Measures

The raw data files generated by Noldus Ethovision listing all XY coordinated and all zones as well as distance traveled and velocity for each frame were used to extract data describing excursions and locomotor patterns using custom code, including the duration and number of bouts at different velocities. An excursion is defined as beginning when the mouse leaves the tunnel (In Tunnel zone) and ending when the mouse returns to the tunnel (one round trip). Continuous velocity values in the data were categorized into three velocity classes, *slow*: velocity ≤ 5 equals; *medium*: velocity > 5 ≤ 15; *fast:* velocity > 15. The length of the bout is calculated using the

number of frames in the sequence and all sequences of the same velocity class longer than 3 frames are counted as a single velocity bout.

QUANTIFICATION AND STATISTICAL ANALYSIS

Foraging Behavior

Excursion Data Capture

Our DeepFeats approach for analyzing modularity in foraging was performed as previously described (Hörndli et al., 2019) with some modifications and advances. In our study, mice were tracked with Noldus Ethovision software. Noldus settings were used to define regions of interest in the foraging arena and indicated when the mouse was in each area. To ensure the tracking is equivalent across different mice, a Procrustes transformation of the XY coordinates was performed to put every tracking file in the same coordinate space. The track coordinates were zero'd to the center of the tunnel to the home cage. We then generated custom code in R to parse the raw Noldus tracking files into discrete, round trip home base excursions from the home cage tunnel. Each excursion is assigned a unique ID key that we call the Concise Idiosyncratic Module Alignment Report (CIMAR) string key. It stores the coordinates of the excursion in the data and the CIMAR string includes metadata regarding the mouse number, excursion number, sex, age, genotype and phase. Next, custom code compares the CIMAR coordinates to the raw Noldus data files and constructs a new dataset that extracts 57 measures from the Noldus output, which we use to initially statistically describe each excursion. The 57 measures are presented in described (Hörndli et al., 2019) and are designed to capture a relatively comprehensive array of different behavioral and locomotor parameters, as well as describe interactions with food and non-food containing patches and exposed regions in the environment. These measures consist of shape, frequency, order and location statistics of an animal's X and Y movements, numbers of visits and time spent at different features in the arena, including food patches (Pots#2 and 4), non-food containing patches (Pots#1 and 3), the tunnel zone, wall zone and center zone of the arena and data describing locomotor patterns, including velocity, gait and distance traveled. The 57 measures for each excursion are scaled (normalized and centered across excursions) because they are in different units.

Behavioral Measures to Resolve Modularity in Excursions

This section details the methods to define the set of behavioral measures that best resolve candidate modules. A data matrix was constructed in which the rows are excursions performed by the mice, labeled by CIMAR keys, and the columns are the 57 behavioral measures. Dimension reduction was performed using Principal Component Analysis and the number of principal components (PCs) to retain for the identification of modules was defined based on the set that maximized cluster identification in the training dataset partition. Unsupervised clustering was performed on the retained PCs. We used the Ward.D2 minimum variance method implemented

using the “hclust” function in R to perform the clustering and define compact, spherical clusters. We then statistically define discrete excursion clusters from the results using the Dynamic Tree Cut algorithm (Langfelder et al., 2008). This is a powerful approach because it is adaptive to the shape of the dendrogram compared to typical constant height cutoff methods and offers the following advantages: (1) identification of nested clusters; (2) suitable for automation; and (3) can combine the advantages of hierarchical clustering and partitioning around medoids, giving better detection of outliers. We detect clusters using the “hybrid” method and use the DeepSplit parameter set to 4 and the minimum cluster size set to 20. The total number of clusters detected is quantified at each correlation threshold. Conceptually, more relaxed correlation threshold cutoffs could reduce cluster detection by retaining redundant measures that mask important effects from other measures. On the other hand, thresholds that are too stringent could reduce cluster detection by pruning informative measures. Our objective is to identify the threshold that uncovers the most informative and sensitive set of measures for resolving different clusters of excursions, setting the stage for the discovery of potential modules.

Statistical Validation of Significant Clusters of Excursions

In our study, Dynamic Tree Cut will deeply cut branches in a dendrogram generating large numbers of small clusters if there are few bona fide relationships in the data. Thus, to test whether bona fide clusters of excursions exist in the data we implemented a random sampling procedure in R in which we randomly sample from the matrix of the retained behavioral measure data to break the relationships between the excursions and the measures. The sampled null data matrix is then subjected to the same clustering and quantification procedure to determine the number of clusters found by Dynamic Tree Cut. A null distribution is created from 10,000 iterations and compared to the observed number of clusters, which is expected to be significantly less than the null due to bona fide biological relationships between the excursions and set of retained measures. A lower tailed p value was computed to test this outcome. In a modification compared our previous study,

IGP Permutation Test

To test whether reproducible modules of behavior exist in the data for the foraging excursions, we use the in-group proportion (IGP) statistical method for testing for reproducible clusters between two datasets (Kapp and Tibshirani, 2007). We built a modified version of this function for parallelized computing to speed the analysis for large numbers of permutations. The excursion data for the mice is separated into a training data and test data partition for reproducibility testing. A balanced partition was generated according to genotype, sex and phase factors using the “createDataPartition” function in the caret package in R. Unsupervised hierarchical clustering was performed on the Training data partition excursions and clusters were defined using Dynamic Tree Cut. Next, the centroids for each training data cluster were computed as the mean values of the behavioral data for the excursions in the cluster. The training data centroids were then used to compute the IGP statistic for each training data cluster based on the test partition data, thereby evaluating the reproducibility of each cluster.

In a modification compared to our previous study described (Hörndli et al., 2019), we created a custom IGP permutation test that is based on a distance calculation, rather than the correlation implementation in the

clusterRepro R package. The distance IGP testing framework was written in C++ and speeds the permutation test by many fold and is a more accurate replication of the clustering parameters used in the test data. We used this approach to compute p values for each cluster to determine whether the IGP value is greater than chance. False positives due to multiple testing errors were controlled using the q-value method (Storey, 2002). Modules are thus defined as significantly reproducible training partition excursion clusters ($q < 0.1$). Each module detected was assigned an ID number and individual excursions in the data were annotated based on the module they match to. This approach facilitated quantifications of module expression frequency by the mice.

Statistical Modeling of Module Expression Counts

To statistically evaluate the genetic and parental factors that significantly affect module expression frequency, we used generalized linear modeling functions implemented in R. The hypotheses tested are detailed in the text for each analysis and below. Prior to module-by-module statistical testing, we filtered based on overall variance to remove modules with low expression variance across all mice in the study and reduce multiple testing errors, which is a proven two-step method for analyzing high dimensional data (Bourgon et al., 2010). Following subsequent module-by-module statistical testing, p-values were corrected for multiple testing errors by the q-value method to control the false discovery rate and pi0 was computed to determine true nulls in the data (Storey and Tibshirani, 2003). In all cases, true nulls included less than half of the modules in the data.

Generalized linear models were fit to maternal or paternal cross data for sons or daughters using the *glm* function in R with the factor of Genotype (levels: wildtype, knockout). The anova function in R was then used to generate Analysis of Deviances Tables with p-values to determine whether genotype main effect explained a significant amount of the variance in the module count data. Generalized linear modeling was performed using a Poisson distribution. We tested the goodness-of-fit of the Poisson for each module with a chi-square test of the residual deviance and degrees of freedom in R. If the goodness-of-fit test indicated the data fit the Poisson model ($p > 0.05$), we proceeded. All modules passed the goodness-of-fit test.

Statistical Modeling of Module Transitions

To statistically evaluate transitions between modules, the start time for each expressed module was recorded. We then constructed 1-step transition matrixes that relate the expressed module to the next expressed module to examine sequences of module expression. To determine whether module expression transitions are dependent on the identity of the previously expressed module, we performed a Fisher's Exact test on the transition count matrix. To compare wild-type and knockout mouse transition matrices, we computed the stationary probability distribution and then the Euclidean distance between the male versus female distribution. Next, we compared the observed distance to a distribution of distances derived from randomly permuted data. In the permutation test, modules are randomly sampled from the wild-type and knockout data, two transition matrices are generated, the stationary probability distribution is computed and then compared by Euclidean distance. The observed distance is compared to the permuted distribution (>10,000 permutations) to determine the p-value.

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FIGURE LEGENDS

FIGURE 1. Mice show a discrete "second-guessing" behavioral stage that involves repeatedly investigating a learned food depleted patch during naturalistic foraging.

(**A** and **B**) Schematic summaries of the Exploration (A) and Foraging (B) phases of our naturalistic foraging assay. During the 30-minute Exploration phase (A), naïve mice learn Pot2 is a food-containing patch. During the 30-minute Foraging phase performed 24hrs later, the food patch has been moved and is now located in Pot4. The mice show a memory response to the former food location.

(**C**) The plot shows the average time spent at the former food patch (Pot2) and the new food patch (Pot4) in the Foraging phase for male (blue) and female (red) mice (n=15). The time at each Pot is shown for 1 minute time bins over the 30-minute testing period. Male and female mice show an initial wave of memory response behavior involving interactions with Pot2 (Stage 1), followed by a second wave (Stage 2) and then decreased interactions (Stage 3). Stars indicate peak interactions and lollypops indicate drops in interaction that delineate Stage 2 boundaries. The plot below shows interactions with the new food patch (Pot4) and reveals a different pattern in which interactions increase steadily during Stages 1 and 2 and persist at high levels during Stage 3.

(**D and E**) The top plots compare the total mean time at the former food patch (Pot2, orange) to time at a non-food containing control patch (Pot1, dark grey) during memory response Stages 1, 2 and 3 for males (D) and females (E) in 1-min time bins (similar to C). Purple lines indicate drops in Pot2 interactions that delineate the Stage 2 boundaries. The bottom plots show the cumulative time at Pot2 and Pot1 during each stage, where solid lines show the mean cumulative and dashed lines show the standard error of the mean (SEM) for the mice tested (n=15). In males (D) and females (E), a significant increase in cumulative time spent at the former food patch (Pot2) is observed during Stage 1 and Stage 2, but not Stage 3, which shows significant memory response behaviors to the former

food during the first two stages only (generalized linear model). Stars indicate the peaks for Stages 1 and 2.

(**F**) The plots show the percentage of the total food that is consumed during the Exploration and Foraging phases by males (blue) and females (pink). The data show that the mice eat less than 20% of the total food, despite being fasted (n=15). Thus, the Stage 2 memory response involving repeated searching of the former food patch (Pot2) in the Foraging phase is not caused by running out of food in Pot4. Mean ± SEM.

(**G and H**) The plots show the cumulative time at the new (Pot4, green) versus former (P2, red) food patches for males (G) and females (H) during Stage 1 of the Foraging phase. The data show that mice rapidly discover and value the new food patch during Stage 1, showing significantly increased cumulative time at the new versus former patch (n=15, generalized linear model). Therefore, the Stage 2 investigations of the former food patch (Pot2) are not caused by a failure to rapidly identify food. Mean±SEM.

(**I and J**) The data show results of generalized linear model testing of whether the cumulative time spent at the former food patch (Pot2) over the entire Foraging phase (TOTAL) or during Stage 2 only (STAGE 2) is significantly affected by a 4hr versus 24hr memory consolidation gap between the Exploration and Foraging phases in male and/or female mice. Statistical results show that significant effects of the consolidation timing (timing) are not observed in total or in Stage 2, nor are there significant interactions with sex. The plots show the data for males (I) and females (J). Mean±SEM, n=15.

FIGURE 2. ARC knockout mice show grossly intact initial memory responses, but significant changes to later stage memory responses.

(**A**) Schematic summary of experimental testing of naturalistic foraging phenotypes in *Arc*$^{-/-}$ versus $^{+/+}$ mice. The experiment tests behaviors related to exploitations of the available food-rich patch (Pot4) versus now food-absent former food patch (Pot2).

(**B**) The plots show the latency to enter the foraging arena from the home during the Exploration (blue) versus Foraging (purple) phases for *Arc*$^{-/-}$ versus $^{+/+}$ littermates. Male and female *Arc*$^{-/-}$ and $^{+/+}$ mice show a significantly reduced latency to enter the arena in the Foraging phase compared to the Exploration phase (n=15). t-test. Mean ± SEM

(**C** and **D**) The bar plots show the total time spent at each of the pots during the first 5 minutes of the Foraging phase for male (C) and female (D) *Arc*$^{-/-}$ mice (orange) and $^{+/+}$ (black) littermates. *Arc*$^{-/-}$ and $^{+/+}$ littermates spend significantly increased time at the former food patch (Pot2), showing they learned and recall this former food patch, and at the new food rich patch (Pot4). A significant main effect of Pot was observed ($p<0.0001$). The +/+ and -/- mice are not significantly different ($p>0.05$). N=15, Mean ± SEM, one-way ANOVA with Tukey post-test. *$p<0.05$, **$p<0.01$, ***$p<0.0001$

(**E** and **F**) Plots of the cumulative time at Pot2 during the Foraging phase show that *Arc*$^{-/-}$ males (E) and females (F) exhibit later stage behavioral changes compared to +/+ controls by spending less time at Pot2 beginning at ~10 min into the Foraging phase (grey dashed line). P-values from generalized linear modeling of cumulative time at 30 min are shown and indicate a significant main effect of genotype (p.geno), but no effect of sex (p.sex) or interaction (p.sex*geno). N=15, Mean ± SEM.

FIGURE S1. Related to Figure 2. *Arc*$^{-/-}$ mice do not show significant changes to food intake or interactions with the food patch (Pot2) during the naïve Exploration phase.

(A) Schematic summary of the Exploration phase.

(B) The plot shows the total food consumed by *Arc*$^{-/-}$ (orange) versus $^{+/+}$ (black) mice in the Exploration phase. A significant difference is not observed. N=15, One-way Anova.

(C) The plot shows total time at the food patch during the Exploration phase (Pot2) broken down by 1 minute time bins. A significant difference is not observed between *Arc*$^{-/-}$ and $^{+/+}$ mice. N=15, mean+SEM, KS test comparison of distributions.

(D) The plots show the time at Pot2 (current food patch) versus Pot4 (future Foraging phase food patch) in the Exploration phase. The average time is plotted from all mice tested and shows a strong preference for the food patch (Pot2) over the patch without food (Pot4). N=15.

FIGURE 3. *Arc*$^{-/-}$ mice show deficits in second-guessing behavior.

(**A** and **B**) The barplots show data for the time spent at the former food patch (Pot2) in the Foraging phase in 1 minute time bins for *Arc*$^{-/-}$ (orange) males (**A**) and females (**B**) compared to +/+ littermate controls (grey). The 1, 2 and 3 memory response stages are delineated by purple numbers and dashed lines. The data show significant loss of the stage 2 second-guessing memory response in *Arc*$^{-/-}$ males and females. Significant changes to Stage 1 and 3 behaviors were not observed. Plots below summarize the phenotypic effect by showing the mean time for knockouts versus wildtypes at Pot2 over the Foraging phase (grey). P-values for generalized linear model are shown on the top. (n=15)

(**C**) The plots show the total food consumed by male and female mice in the Exploration (Exp) phase and Foraging (For) phase for *Arc*$^{-/-}$ (orange) mice compared to +/+ littermate controls (grey). Males show significantly increased food consumption in the Foraging phase. N=15, Generalized linear model interaction for phase and food consumed.

(**D** and **E**) The barplots show data for the time spent at the new food patch (Pot4) in the Foraging phase in 1 minute time bins for *Arc*$^{-/-}$ (orange) males (**F**) and females (**G**) compared to +/+ littermate controls (grey). Male *Arc*$^{-/-}$ mice show increased time at the food patch specifically during the Stage 2 second-guessing memory response. N=15, Mean $\pm$ SEM.

FIGURE S2. Related to Figure 4. Identification of foraging modules.

(**A**) The plot shows the number of principle components (PCs) and proportion of variance explained by each PC. The chosen PC cutoff is in orange at the elbow of the plot and captures 76% of variance

in the data for hundreds of measures describing discrete round trip foraging excursions from the home.

(**B**) The plot shows the number of clusters discovered with the selected PCs based on different cutoffs for the number of PCs chosen. The data reveal that the maximum cluster number and minimum standard deviation in terms of cluster number is achieved using 8 PCs.

(**C**) Shows the DeepFeats training and testing partitions and clustering results to identify behavioral modules. Dynamic tree cutting yielded 43 candidate clusters in the training data for module testing.

(**D**) The pie charts show the number of significant modules (red) versus training set clusters that are not modular (grey) (ie. Significantly reproducible in the test data). The number of round trip excursions found to be modular (red) versus non-modular (grey) is shown below. In-group proportion permutation test, Q-value <0.1.

FIGURE 4. Loss of *Arc* affects the expression of discrete foraging modules that underlie second-guessing versus feeding behaviors.

(**A and B**) The heatmaps show transition matrices for module expression sequences during foraging behaviors in the Exploration and Foraging phase in males (A) and females (B). The y-axis shows Module State 1 and x-axis is Module State 2, where the intersections are the transition frequencies in a heatmap that shows module-to-module transition frequencies. Module expression transitions are significantly stereotyped and non-random in the Exploration and Foraging phases in $Arc^{-/-}$ and +/+ mice (Fisher's Exact Test of dependency, p-value shown above matrix; a trend is observed in males during Exploration phase). Grey rows are modules that are not expressed due to being specific to either the Exploration or Foraging phases. (n=15)

(**C-F**) The plots show results of a permutation test comparing the transition matrices between Arc +/+ versus -/- mice in the Exploration (EXP, C and E) and Foraging (FOR, D and F) phases for males (C and D) and females (D and F). The permutation test compares the stationary probability distributions of the transition matrices for $Arc^{-/-}$ and $^{+/+}$ mice. The results show a significant difference in module

expression transitions between *Arc*$^{-/-}$ and $^{+/+}$ mice specifically in the Foraging phase in males and females. TVD, total variation distance between transition matrices stationary distributions.

(**G-I**) The heatmaps show the total expression frequency of different foraging modules (rows) in male and female *Arc* KO (-/-) and WT (+/+) mice (columns). Unsupervised hierarchical clustering of the data grouped male and female KOs separately from WTs in memory response Stages 2 (H) and 3 (I), but not Stage 1 (G). A chi-square test on the Stage 2 and 3 datasets showed statistical significance (p-value shown on top), indicating significant dependence of genotype on module expression. The data reveal that specific Modules are most strongly affected, including Module 1, which has increased expression in KO mice, and Module 21, which shows decreased expression in KO mice (highlighted in orange). Insets show traces of representative foraging movement patterns for Module 1 and Module 21, including side angle and top-down views. The locations of the home (H), Pot1(1), Pot2(2, former food), Pot3 (3) and Pot4(4) are shown. The movement is colored according to gait velocity (slow: darker; fast: light purple).

Figure 1

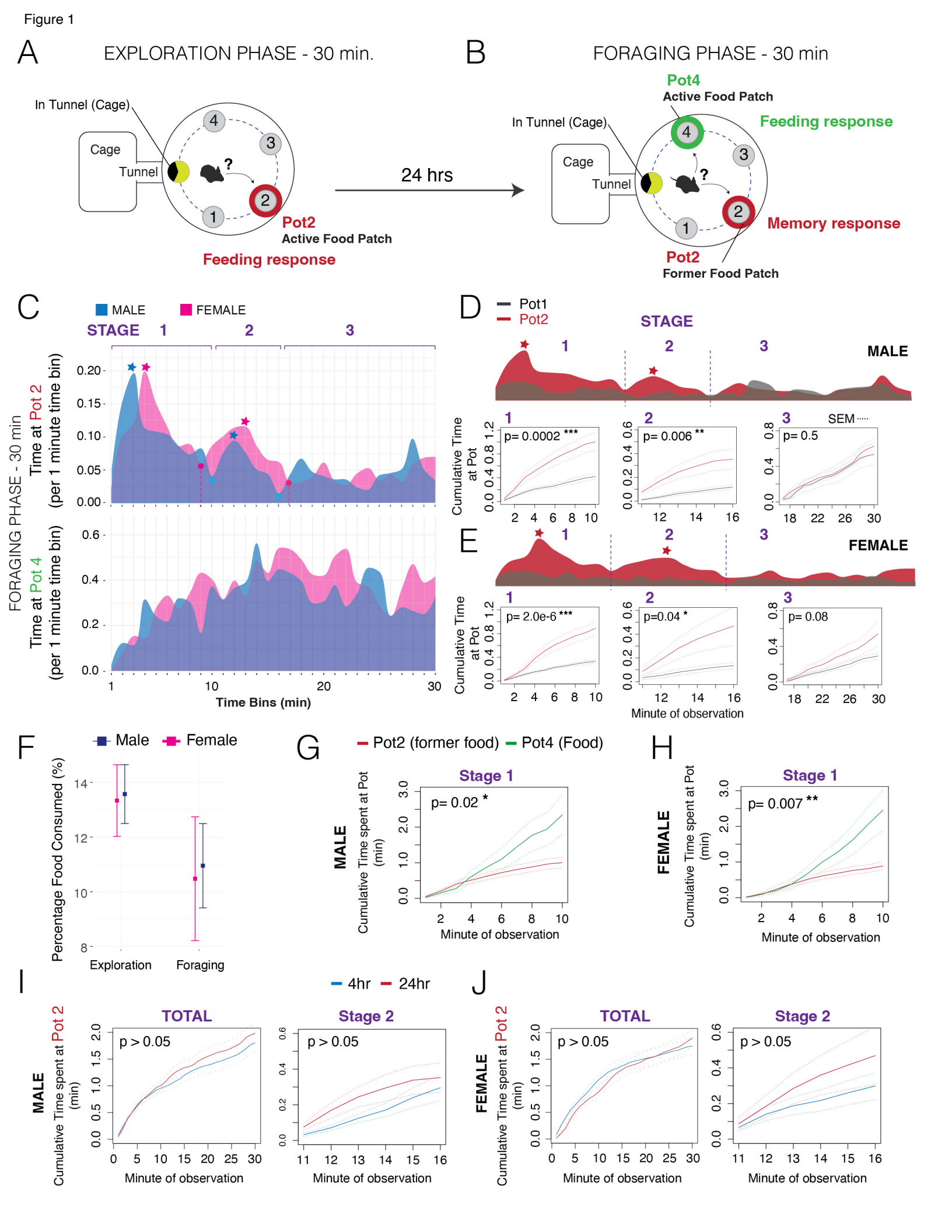

A
EXPLORATION PHASE - 30 min.
In Tunnel (Cage)
Cage
Tunnel
Pot2
Active Food Patch
Feeding response
24 hrs
B
FORAGING PHASE - 30 min
Pot4
Active Food Patch
Feeding response
Memory response
Pot2
Former Food Patch
C
MALE
FEMALE
STAGE
FORAGING PHASE - 30 min
Time at Pot 2 (per 1 minute time bin)
Time at Pot 4 (per 1 minute time bin)
Time Bins (min)
D
Pot1
Pot2
STAGE
MALE
Cumulative Time at Pot
p= 0.0002 ***
p= 0.006 **
p= 0.5
SEM
E
FEMALE
p= 2.0e-6 ***
p=0.04 *
p= 0.08
Minute of observation
F
Male
Female
Percentage Food Consumed (%)
Exploration
Foraging
G
Pot2 (former food)
Pot4 (Food)
Stage 1
MALE
Cumulative Time spent at Pot (min)
p= 0.02 *
Minute of observation
H
FEMALE
p= 0.007 **
I
4hr
24hr
TOTAL
Stage 2
p > 0.05
J

Figure 2

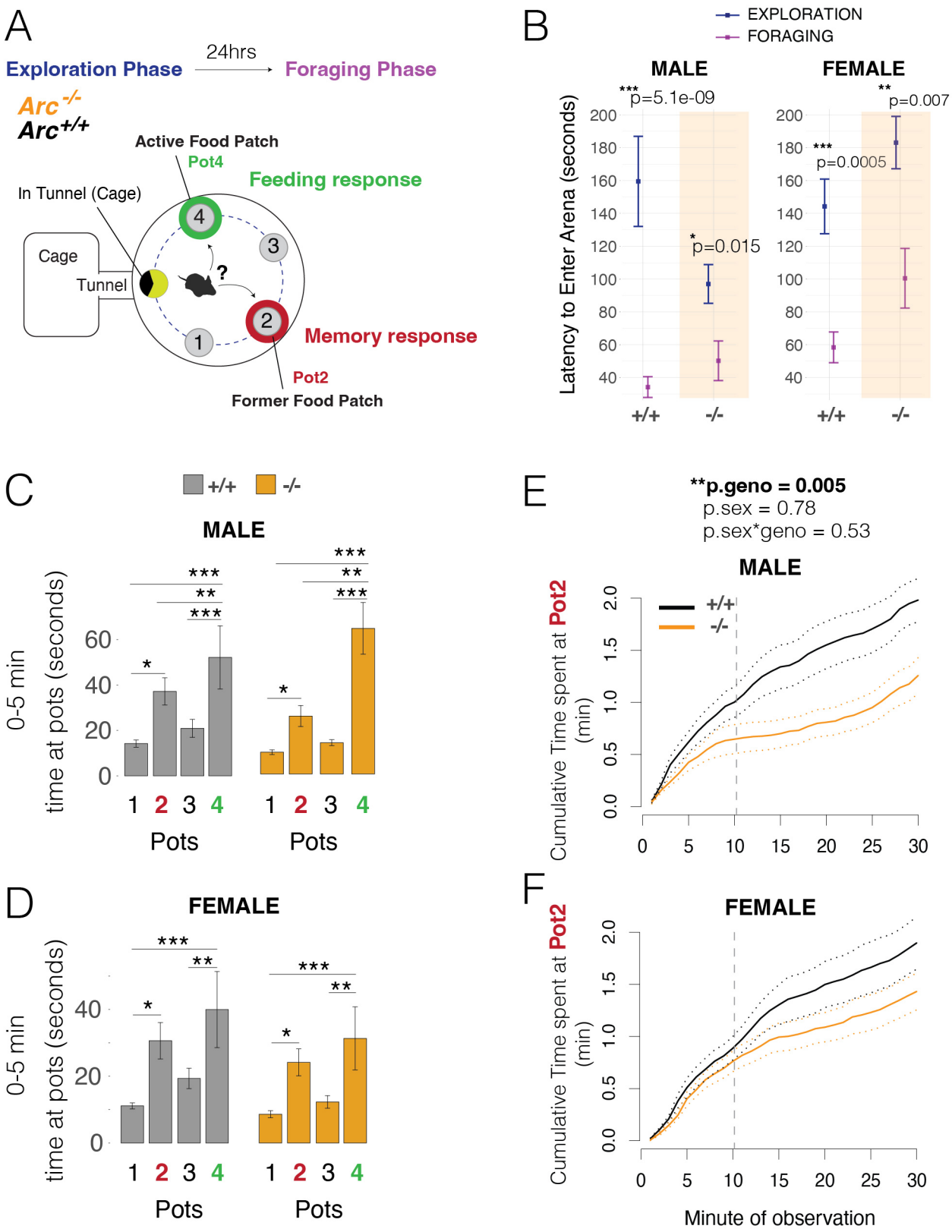

A
Exploration Phase
24hrs
Foraging Phase
Arc -/-
Arc+/+
Active Food Patch
Pot4
Feeding response
In Tunnel (Cage)
Cage
Tunnel
Memory response
Pot2
Former Food Patch
B
EXPLORATION
FORAGING
MALE
FEMALE
Latency to Enter Arena (seconds)
***p=5.1e-09
*p=0.015
**p=0.007
***p=0.0005
+/+
-/-
C
+/+
-/-
MALE
0-5 min time at pots (seconds)
Pots
D
FEMALE
E
**p.geno = 0.005
p.sex = 0.78
p.sex*geno = 0.53
Cumulative Time spent at Pot2 (min)
F
Minute of observation

Figure S1

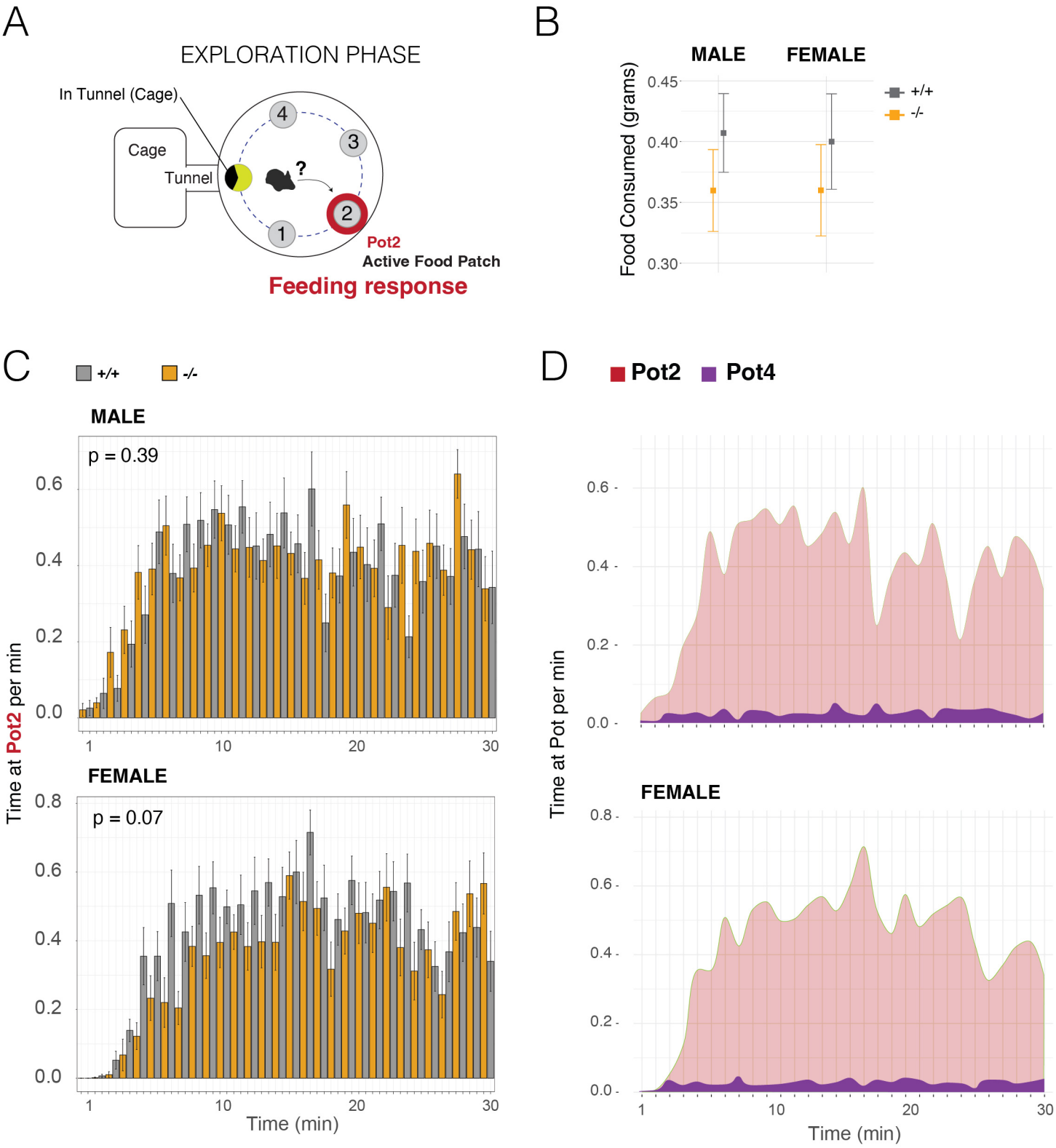

A
EXPLORATION PHASE
In Tunnel (Cage)
Cage
Tunnel
4
3
2
1
?
Pot2
Active Food Patch
Feeding response
B
MALE
FEMALE
Food Consumed (grams)
0.45
0.40
0.35
0.30
+/+
-/-
C
+/+
-/-
MALE
p = 0.39
FEMALE
p = 0.07
Time at Pot2 per min
Time (min)
D
Pot2
Pot4
FEMALE
Time at Pot per min
Time (min)

Figure 3

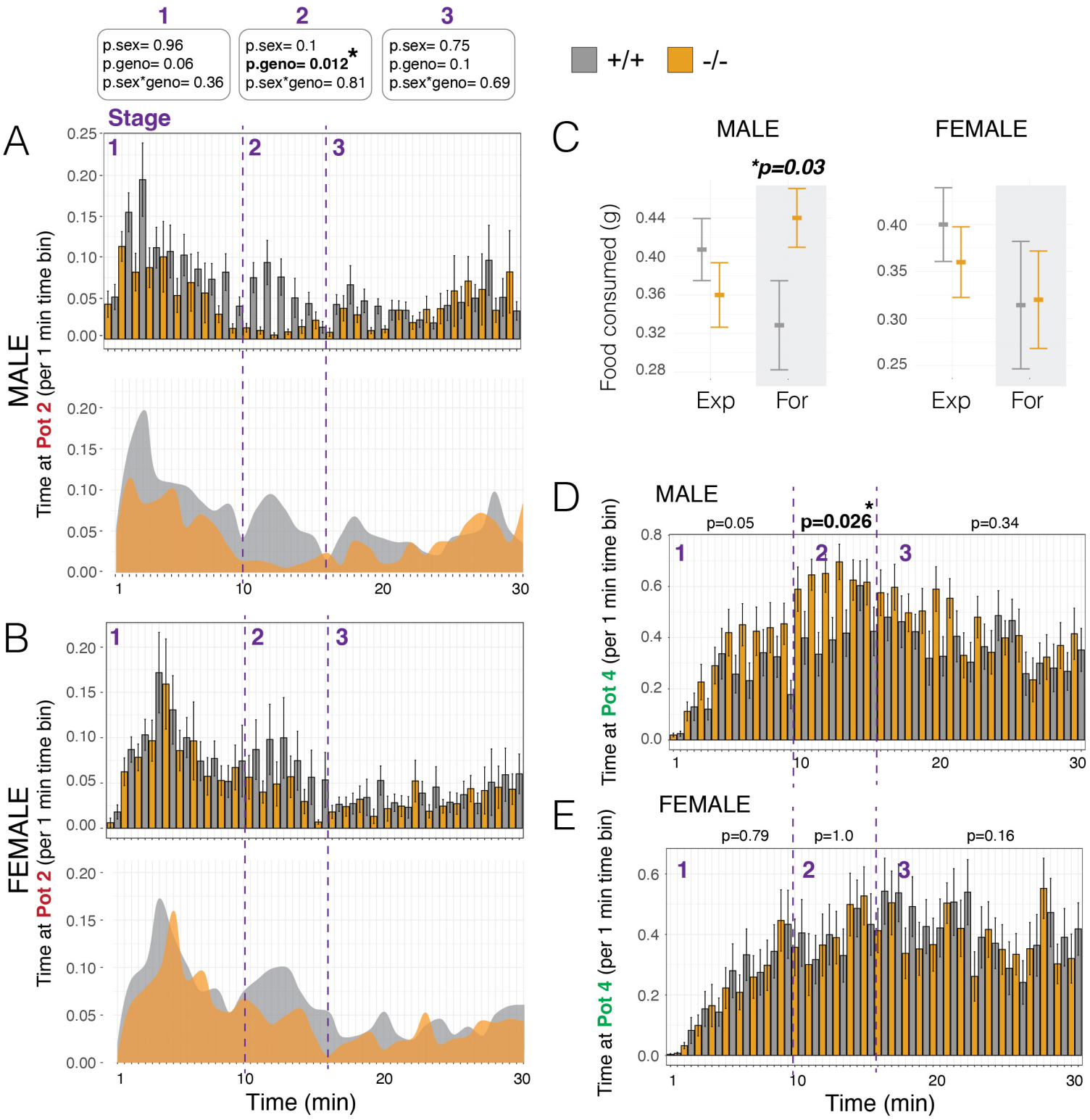

1
p.sex= 0.96
p.geno= 0.06
p.sex*geno= 0.36
2
p.sex= 0.1
p.geno= 0.012*
p.sex*geno= 0.81
3
p.sex= 0.75
p.geno= 0.1
p.sex*geno= 0.69
+/+
-/-
A
Stage
MALE
Time at Pot 2 (per 1 min time bin)
B
FEMALE
Time at Pot 2 (per 1 min time bin)
Time (min)
C
MALE
FEMALE
*p=0.03
Food consumed (g)
Exp
For
D
MALE
p=0.05
p=0.026*
p=0.34
Time at Pot 4 (per 1 min time bin)
E
FEMALE
p=0.79
p=1.0
p=0.16
Time at Pot 4 (per 1 min time bin)
Time (min)

Figure 4

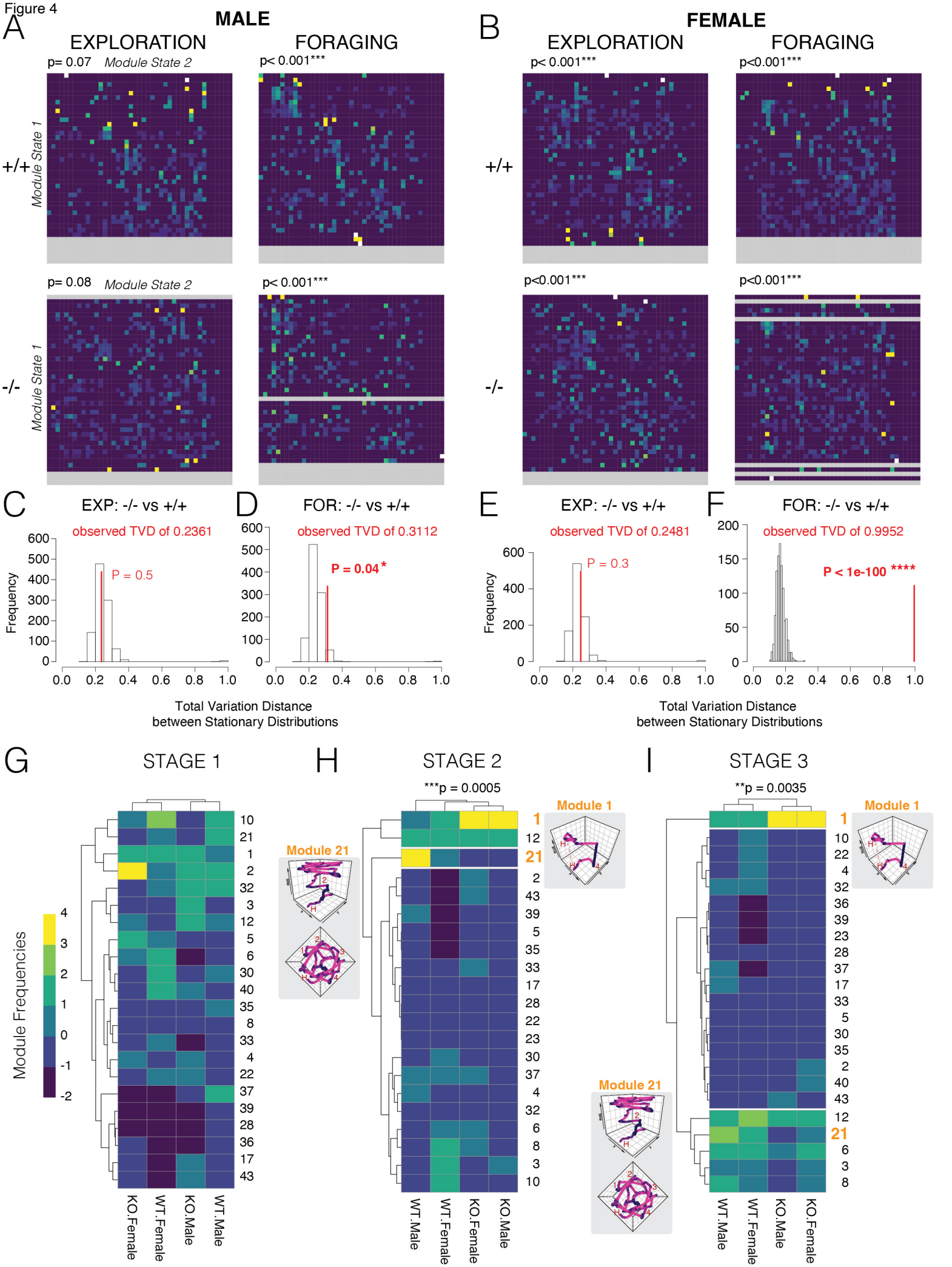
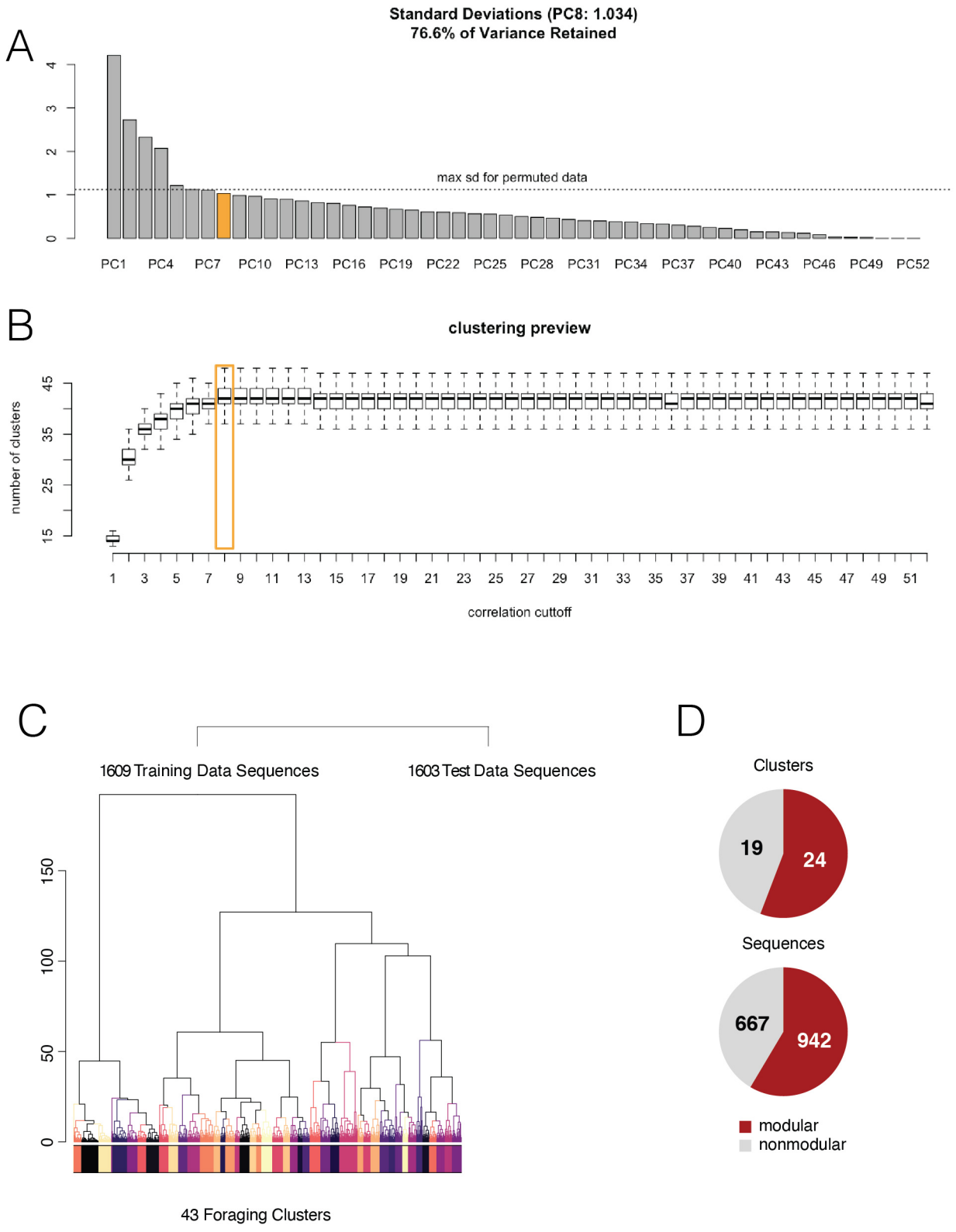

A
MALE
EXPLORATION
FORAGING
p= 0.07
Module State 2
p< 0.001***
+/+
Module State 1
p= 0.08
Module State 2
p< 0.001***
-/-
Module State 1
B
FEMALE
EXPLORATION
FORAGING
p< 0.001***
p<0.001***
+/+
p<0.001***
p<0.001***
-/-
C
EXP: -/- vs +/+
observed TVD of 0.2361
P = 0.5
Frequency
D
FOR: -/- vs +/+
observed TVD of 0.3112
P = 0.04*
E
EXP: -/- vs +/+
observed TVD of 0.2481
P = 0.3
Frequency
F
FOR: -/- vs +/+
observed TVD of 0.9952
P < 1e-100 ****
Total Variation Distance
between Stationary Distributions
Total Variation Distance
between Stationary Distributions
G
STAGE 1
Module Frequencies
KO.Female
WT.Female
KO.Male
WT.Male
H
STAGE 2
***p = 0.0005
Module 21
Module 1
WT.Male
WT.Female
KO.Female
KO.Male
I
STAGE 3
**p = 0.0035
Module 1
Module 21
WT.Male
WT.Female
KO.Male
KO.Female

Figure S2


A
Standard Deviations (PC8: 1.034)
76.6% of Variance Retained
max sd for permuted data
PC1 PC4 PC7 PC10 PC13 PC16 PC19 PC22 PC25 PC28 PC31 PC34 PC37 PC40 PC43 PC46 PC49 PC52
B
clustering preview
number of clusters
correlation cuttoff
C
1609 Training Data Sequences
1603 Test Data Sequences
43 Foraging Clusters
D
Clusters
19
24
Sequences
667
942
modular
nonmodular