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# Postmeal optogenetic inhibition of dorsal hippocampal principal neurons increases future intake in a time-dependent manner

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ABSTRACT

Research involving human participants indicates that memories of recently eaten meals limit how much is eaten during subsequent eating episodes; yet, the brain regions that mediate the inhibitory effects of ingestion-related memory on future intake are largely unknown. We hypothesize that dorsal hippocampal (dHC) neurons, which are critical for episodic memories of personal experiences, mediate the inhibitory effects of ingestion-related memory on future intake. Our research program aimed at testing this hypothesis has been influenced in large part by our mentor James McGaugh and his research on posttraining manipulations. In the present study, we used an activity-guided optogenetic approach to test the prediction that if dHC glutamatergic neurons limit future intake through a process that requires memory consolidation, then inhibition should increase subsequent intake when given soon after the end of a meal but delayed inhibition should have no effect. Viral vectors containing CaMKIIα-eArchT3.0-eYFP and fiber optic probes were placed in the dHC of male Sprague-Dawley rats. Compared to intake on a day when no inhibition was given, postmeal inhibition of dHC glutamatergic neurons given for 10 min after the end of a saccharin meal increased the likelihood that rats would consume a second meal 90 min later and significantly increased the amount of saccharin solution consumed during that next meal when the neurons were no longer inhibited. Importantly, delayed inhibition given 80 min after the end of the saccharin meal did not affect subsequent intake of saccharin. Given that saccharin has minimal postingestive gastric consequences, these effects are not likely due to the timing of interoceptive visceral cues generated by the meal. These data show that dHC glutamatergic neural activity is necessary during the early postprandial period for limiting future intake and suggest that these neurons inhibit future intake by consolidating the memory of the preceding meal.

## 1. Introduction

Memories of recently eaten meals influence subsequent eating episodes (Higgs & Spetter, 2018). For example, when considering what and how much to eat from a restaurant menu for lunch, we may rely on past experiences from this restaurant and our recollections of whether we ate a big, small, healthy or unhealthy breakfast earlier that day. Memories of recently eaten meals can serve as a powerful mechanism for controlling future eating behavior by creating a record of recent intake that likely outlasts most physiological signals generated by ingestion. In support, evidence from human studies suggests that impairing the memory of a meal increases intake during the next eating episode and that enhancing meal-related memory has the opposite effect (Higgs & Spetter, 2018). Patients with amnesia do not remember eating and will eat an additional meal when presented with food, even when they have just eaten to satiety (Hebben, Corkin, Eichenbaum, & Shedlack, 1985; Higgs, Williamson, Rotshtein, & Humphreys, 2008; Rozin, Dow, Moscovitch, & Rajaram, 1998). Moreover, episodic memory deficits are associated with uncontrolled eating in healthy adults (Martin, Davidson, & McCrory, 2018).

The brain regions that mediate the inhibitory effects of ingestion-related memory on future intake are largely unknown. We hypothesize that dorsal hippocampal (dHC) neurons, which are critical for episodic memories of personal experiences (Barbosa, Pontes, Ribeiro, Ribeiro, & Silva, 2012; Drieskens et al., 2017; Hunsaker, Lee, & Kesner, 2008; Panoz-Brown et al., 2018; Zhou, Hohmann, & Crystal, 2012), mediate the inhibitory effects of ingestion-related memory on future intake. To begin to test this hypothesis, we drew our inspiration from

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James L. McGaugh's research on posttraining manipulations. As a graduate student, McGaugh was influenced heavily by his mentor, the legendary cognitive psychologist Edward Tolman. In particular, McGaugh took to heart Tolman's assertion that learning was inferred from behavioral performance, and importantly, that the task of the researcher was to isolate the contributions of learning from any change in performance (Tolman, 1930). This is no easy feat as many non-mnemonic factors influence performance on a behavioral test (McGaugh, 1989). He also took clues from a) Mueller and Pilzecker's notion that a memory trace is fragile after learning (Muller & Pilzecker, 1900), b) Donald Hebb's proposal that learning induces reverberating activity in the brain essential for establishing neural connections underlying the memory of that learning (Hebb, 1949), and c) Carl Duncan's finding that electroconvulsive shock given to rats *after* training impaired subsequent retention performance (i.e., produced retrograde amnesia; (Duncan, 1949). Based on this collective evidence, he hypothesized that one should be able to enhance or impair the consolidation of a memory by administering a drug immediately after learning. He reasoned further that posttraining manipulations would resolve the learning-performance problem by ensuring that an animal was not under the influence of a drug during training or on the memory test. In what he describes as one of the most euphoric moments in his scientific career, McGaugh discovered that posttraining injections of strychnine enhanced memory in rats (McGaugh & Petrinovich, 1965; Squire, 2003). McGaugh spent the next phase of his remarkable research career demonstrating that a variety of peripheral and central manipulations given immediately after training in several different appetitively- and aversively-motivated behavioral tasks enhanced and impaired subsequent retention performance in a dose-dependent manner (McGaugh, 1966, 1989, 2000).

Inspired by these findings, we set out to determine whether dHC neurons mediate the inhibitory effects of ingestion-related memory on future intake by 1) determining whether ingestion influences dHC neural activity during the early postprandial period and 2) whether *postmeal* inhibition of dHC neurons increases subsequent intake. In support, we found that ingestion induces the posttranslational modifications and gene activation events necessary for synaptic plasticity and memory in dHC neurons during the early postprandial period. Specifically, consuming a sucrose meal increases phosphorylation of glutamate AMPA receptor GluA1 subunits at serine 831 sites in dHC neurons (Ross, Barnett, Faulkner, Hannapel, & Parent, 2019) and ingestion of sucrose or the noncaloric sweetener saccharin increases the expression of activity-regulated cytoskeleton-associated protein (*Arc*) in dHC neurons (Henderson, Nalloor, Vazdarjanova, & Parent, 2016). The latter is noteworthy because *Arc* is considered a master regulator of synaptic plasticity that is necessary for memory consolidation (Bramham, Worley, Moore, & Guzowski, 2008; Korb & Finkbeiner, 2011; Shepherd & Bear, 2011).

Our laboratory was the first to show that dHC neurons limit future feeding when we reported that intra-dHC infusions of the GABA agonist muscimol administered immediately following the end of a sucrose meal, when the memory of the meal would presumably be undergoing consolidation, accelerated the initiation of the next meal and doubled the amount rats consumed during that next meal (Henderson, Smith, & Parent, 2013). One concern that remains unaddressed in these results is the learning-performance distinction because muscimol inhibits neural activity for several hours (Majchrzak & Di Scala, 2000; Martin, 1991; Martin & Ghez, 1999), and therefore postmeal inactivation likely persisted throughout the postprandial period, during intake of the next meal, and beyond that. As a result, it is impossible to know whether these postmeal manipulations increased the amount consumed during the next meal by disrupting memory-based processes during the postprandial period or via a non-mnemonic effect on intake during consumption of the second meal. To address this issue and to investigate the specific role of principal dHC neurons, we later used an activity-guided optogenetic approach to inhibit dHC glutamatergic neurons in a temporally precise manner before, during, or after the consumption of a meal (Hannapel et al., 2019). This allowed us to determine when neural activity in these neurons is critical for limiting future intake and to identify whether neural inhibition restricted to the immediate postmeal period would increase subsequent intake at a later time when the neurons were no longer inhibited. Critically, the findings suggested that inactivation given after the end of a chow, sucrose, or saccharin meal significantly increased consumption during the next meal. Moreover, the results implicated the early postprandial period as being critical for influencing future intake because inactivation given before or during intake of the first meal did not affect the amount consumed during that meal or during the next bout (Hannapel et al., 2019).

Another critical observation that McGaugh made early in his career was that the effects of posttraining manipulations are time-dependent, such that the efficacy of posttraining treatments diminishes as the training-treatment interval increases (McGaugh, 1966; McGaugh & Izquierdo, 2000). These findings support the idea that new memories are initially labile and gain stability and permanence through consolidation, and that the period in which posttraining manipulations effectively influence future retention performance delineates the consolidation window for that experience. For example, Parent and McGaugh found that posttraining reversible inactivation of the basolateral complex of the amygdala, but not the central nucleus of the amygdala, impairs memory in a time-dependent manner (Parent & McGaugh, 1994). Similarly, there is extensive evidence indicating that the effects of posttraining dHC manipulations on memory are time-dependent (Izquierdo et al., 1992; Jerusalinsky et al., 1992; Lorenzini, Baldi, Bucherelli, Sacchetti, & Tassoni, 1996; Oliveira, Hawk, Abel, & Havekes, 2010; Riedel et al., 1999). For example, temporarily inactivating dHC with tetrodotoxin (TTX) immediately after inhibitory avoidance training impairs memory tested 48 hr after acquisition; in contrast, dHC infusions of TTX given 6 hr after training have no effect (Lorenzini et al., 1996). Similarly, blocking dHC AMPA, NMDA, or metabotropic glutamate receptors after inhibitory avoidance learning produces retrograde amnesia in a time-dependent manner (Bonini et al., 2003; Jerusalinsky et al., 1992).

In the present report, we tested the hypothesis that dHC neurons influence future intake through a process that requires meal-related memory consolidation by determining whether the effects of postmeal dHC inhibition are time-dependent. We used an optogenetic approach to test the prediction that postmeal inhibition increases subsequent intake when given after the end of a meal and that delayed inhibition has no effect. A saccharin solution served as the meal in the present experiment because it has minimal postingestive gastric consequences (Foletto et al., 2016; Mook, Bryner, Rainey, & Wall, 1980; Renwick, 1985, 1986; Sclafani & Nissenbaum, 1985), which diminished the possibility that any time-dependent effects of postmeal inhibition could be due to the timing of interoceptive visceral cues generated by the meal.

## 2. Materials and methods

### 2.1. Subjects

Adult male Sprague-Dawley rats (8–10 weeks old; N = 15; Charles River Laboratories) were housed singly under a 12:12 hr light–dark cycle and given *ad libitum* access to pelleted food and water. All procedures were performed in accordance with the NIH guidelines for the care of laboratory animals and approved by the Georgia State University Institutional Animal Care and Use Committee.

### 2.2. Stereotaxic surgery

#### 2.2.1. Viral infusion

Rats were anesthetized with 5% isoflurane gas and oxygen (500 ml/min) and anesthesia was maintained with 1–3% isoflurane. Stereotaxic surgical procedures were used to lower a 33-gauge injection needle into the dHC (AP: −3.7 mm, ML: +2.8 mm, DV: −4.0 mm from skull surface

(Paxinos & Watson, 2007). rAAV5-CaMKIIα-eArchT3.0-eYFP (0.5 μl; University of North Carolina Gene Therapy Vector Core) was then infused into one hemisphere (hemisphere counterbalanced across rats) at a rate of 0.125 μl/min. Our previous findings indicate that unilateral inhibition of dHC is sufficient to increase subsequent feeding (Hannapel et al., 2019; Henderson et al., 2013). The injection needle was left in place for 4 min after the end of the infusion to allow for diffusion of the virus. Carprofen (5 mg/kg, sc; Covetrus) was given prior to surgery and 24 hr after surgery and 0.9% sterile saline (3 ml, sc) was given immediately after surgery.

#### 2.2.2. Ferrule implantation

As described elsewhere (Hannapel et al., 2019; Huff, Emmons, Narayanan, & LaLumiere, 2016; Sparta et al., 2011), a fiber optic (200 μm core; ThorLabs) was fitted and glued into a stainless-steel fiber ferrule (Precision Fiber Products). Two weeks after the viral infusions, the ferrule was implanted into the dHC (AP:−3.7 mm, ML:+2.8 mm, DV:−4.0 mm from skull surface (Paxinos & Watson, 2007) and affixed to the skull using three surgical screws and dental acrylic. A plastic dust cap (Precision Fiber Products) was placed on top of each ferrule. The rats were given at least 1 week of recovery prior to behavioral testing.

### 2.3. Optical inhibition

To increase the likelihood that rats would consume the saccharin solution on experimental days and to avoid any issues associated with novelty, the rats were exposed to the saccharin solution (0.2% w/v) for 10 min/day for 3 days and experimental days began on the fourth day. At lights on, the rats were brought to the testing space, placed in experimental cages with water and their ferrules were connected (ADAF2; ThorLabs) to an armored optical commutator (RJPFF2; ThorLabs) that was coupled to a laser (200 mW DPSS laser, 556 nm; Opto Engine LLC) via a FC/PC fiber coupler (Opto Engine LLC). After 3 hr, they were given access to the saccharin solution and allowed to consume for 5 min after they started licking and then the saccharin was removed (see Fig. 2A). dHC neurons were photostimulated (556 nm; 10 mW; 10 min) either 5 min (i.e., IMMEDIATE) or 80 min (i.e., DELAYED) after the first saccharin meal. Ten mW light output produces ~ 1 mW/mm$^2$ of light up to 1 mm from the fiber tip and illumination (556 nm) activates eArchT3.0 in at least 0.4 mm$^3$ of tissue (Yizhar, Fenno, Davidson, Mogri, & Deisseroth, 2011). The saccharin solution was returned 90 min after the completion of the first saccharin meal and left in place for 3 hr. The testing cages were equipped with a modified lickometer system that measured the change in system resistance when a rat licked from a sipper tube (Model 86062, Lafayette Instruments, Lafayette, IN). A saccharin meal was defined as any bout containing at least 30 licks (Hannapel, Henderson, Nalloor, Vazdarjanova, & Parent, 2017; Smith, 2000) and this criterion was applied to the *posthoc* analyses of the licking measures. All sipper tube contacts were assumed to result in ingestion and the amount consumed was estimated indirectly by summing the duration of all sipper tube contacts during the meal. The amount of saccharin solution consumed during the second meal following IMMEDIATE or DELAYED inhibition was compared to intake on a day when the rats were attached to the laser but not given photostimulation (i.e., NONE). A within-subject design was used wherein each rat was given all three conditions in a counterbalanced order with 48 hr separating the three experimental days.

We elected to provide saccharin for 5 min for the first meal based on our previous findings showing that rats complete their first saccharin meal within approximately 5 min when allowed to consume *ad libitum*; the saccharin solution was returned 90 min later given our observation that 90 min is the average interval between a first and second saccharin meal (i.e., the postprandial intermeal interval; (Hannapel et al., 2019 and unpublished data). We waited 5 min after the completion of the first meal to perform the IMMEDIATE manipulation in order to be consistent with our previous research involving postmeal manipulations (Hannapel

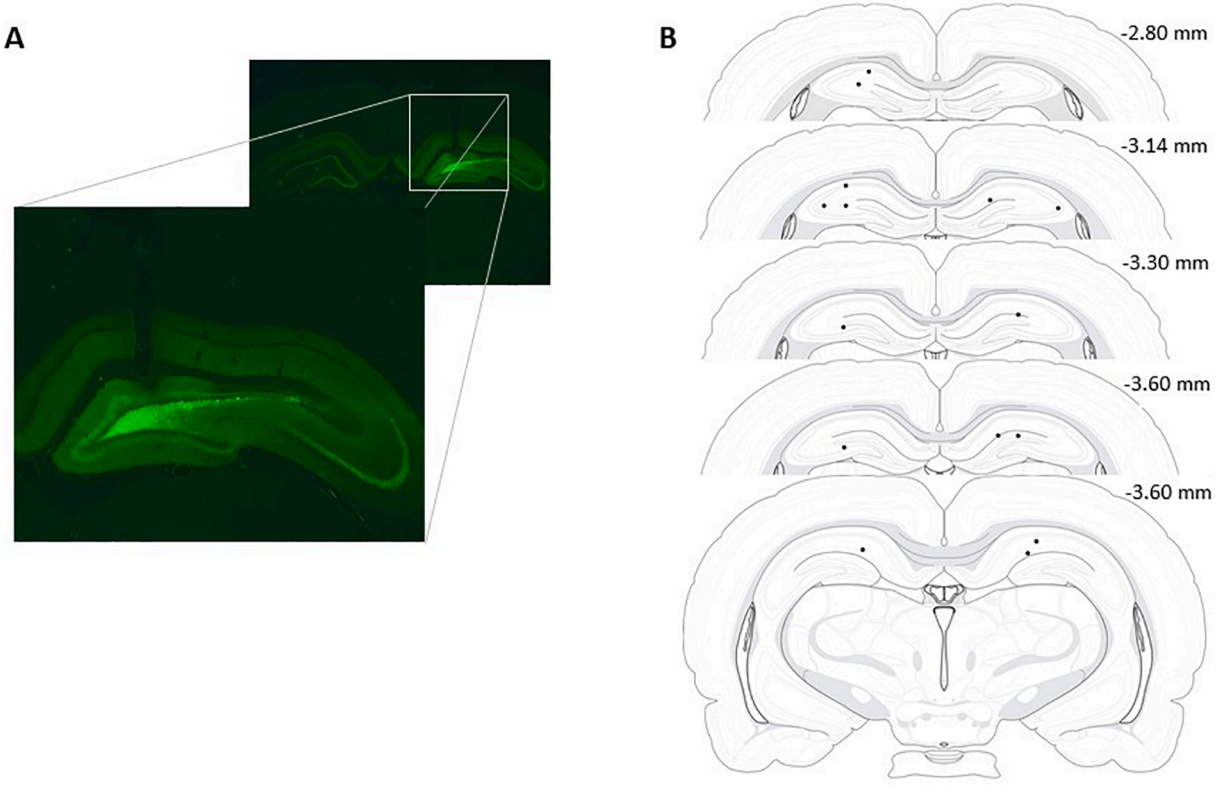


**Fig. 1.** Viral expression and ferrule placement in dHC. A, Representative image depicting viral and ferrule location in dHC. B, Schematic depiction of ferrule placement in dHC relative to bregma (adapted from Brain Maps: Structure of the Rat Brain (Swanson, 2004).

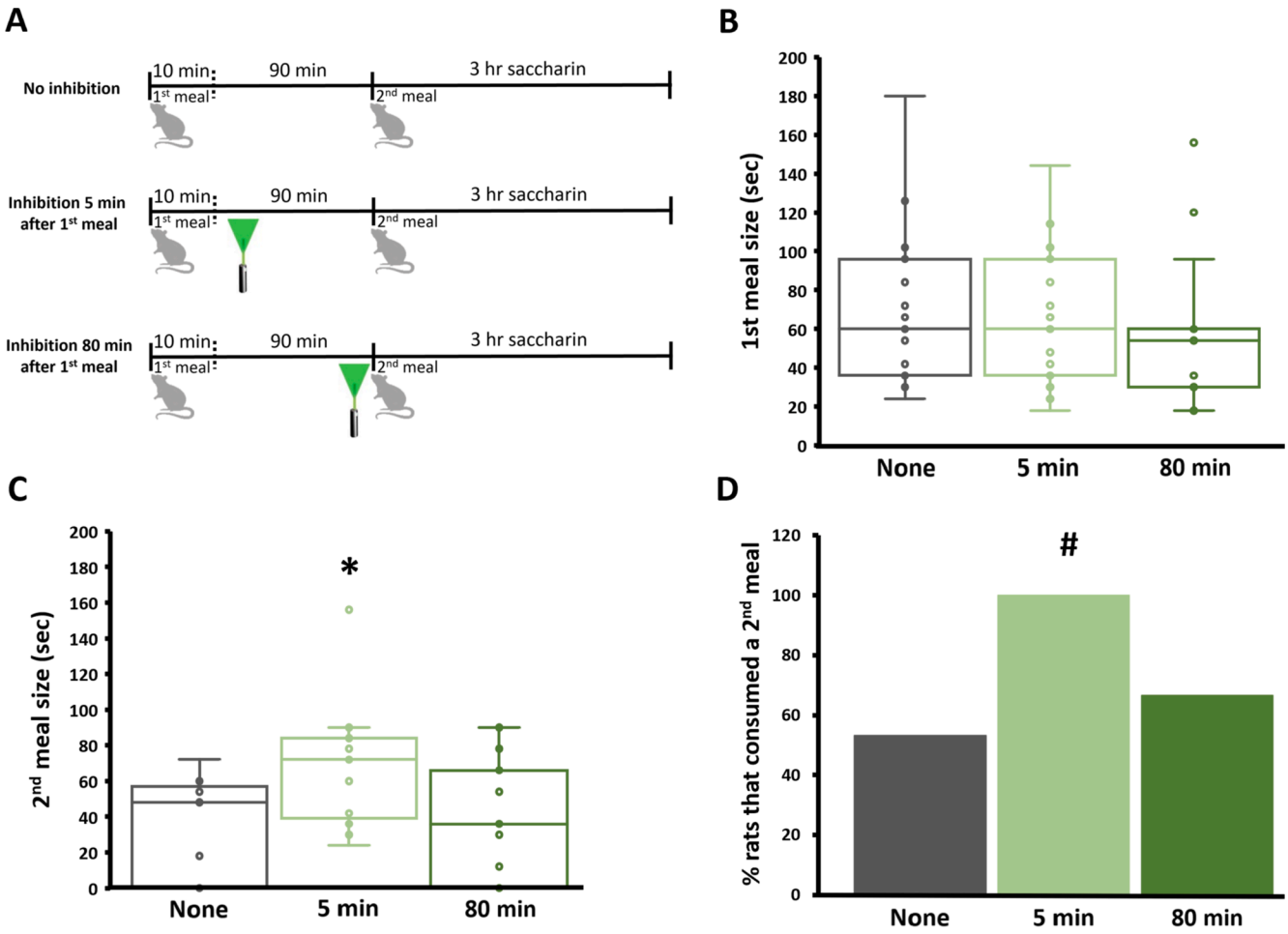


**Fig. 2.** Delayed inhibition of dHC glutamatergic neurons increases future intake in a time-dependent manner. A, Rats were given saccharin on three separate experimental days with different optogenetic treatments given on each day in a counterbalanced order. On one day they were attached to the laser but not given photoillumination (NONE) and on the other two days they were given 10 min of photoillumination either 5 or 80 min after the end of the first saccharin meal. B, Rats consumed similar amounts of saccharin during their first saccharin meal. C, Postmeal inhibition of dHC glutamatergic neurons given 5 min but not 80 min after the first meal increases the amount consumed during the second meal. D, Not all rats ate a second meal. Inhibiting dHC glutamatergic neurons 5 min after the first meal but not 80 min after increases the probability that rats will consume a second meal. *$p < 0.05$; vs. NONE & 80 min; $^{\#}p < 0.05$; vs. NONE; N = 15; within-subject design.

et al., 2019; Hannapel et al., 2017; Henderson et al., 2013). In those previous experiments, rats were given *ad libitum* access to chow, sucrose or saccharin and thus we had to distinguish pauses within a meal from the end of a meal in order to effectively time the postmeal manipulations. Previous work indicates that when rats stop ingesting for 5 consecutive min there is a low likelihood that they will initiate eating again at that time (Fekete et al., 2007; Zorrilla et al., 2005) and a high probability that they will exhibit a progression of active grooming and resting behaviors known as the behavioral satiety sequence (Antin, Gibbs, Holt, Young, & Smith, 1975; Fekete et al., 2007; Kushner & Mook, 1984; Zorrilla et al., 2005). Thus, one significant consequence of this operational definition is that 5 min had to elapse before the experimenter could know that the first meal was terminated, and therefore immediate postmeal inhibition was actually started 5 min after the end of the first meal in our previous work (Ambrogi, Perioli, Ciarnelli, Nocchetti, & Rossi, 2009; Hannapel et al., 2019; Hannapel et al., 2017; Henderson et al., 2013).

### 2.4. Histology

At the completion of the behavioral experiments, rats were perfused transcardially with 4% paraformaldehyde and then the brains were cryopreserved in a solution containing 30% ethylene glycol with 15% sucrose before being sectioned (40 μm) and mounted onto gelatin-subbed slides. Images of viral expression and ferrule placement were evaluated by an observer blind to treatment condition using a fluorescence microscope (Axio Zoom V16; Zeiss) and only the data from rats that had fluorescence and ferrules within the dHC were included in the statistical analyses.

### 2.5. Statistical analyses

All statistical analyses and graphs were generated using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corporation) and Excel (Microsoft Corporation). Normality and homogeneity of variance were tested using Shapiro-Wilkes and Bartlett's tests, indicating that the size of the first meal and second meal were not normally distributed and required non-parametric analyses. Therefore, Friedman tests and Bonferroni multiple comparisons *post hoc* tests were used to analyze these measures, and the data were represented as box-and-whiskers plots. A McNemar's chi-squared test was conducted to analyze the percentage of rats that consumed a 2nd meal.

## 3. Results

Seven rats were excluded due to low or no viral expression, five rats

were excluded from the analyses because they did not consume any saccharin solution on one of the three experimental days, and the data from three rats were excluded because the size of their first meal was more than two standard deviations from the mean resulting in a final sample size of 15 rats. Fig. 1 shows a representative image of viral expression (Fig. 1A) and a schematic depiction of ferrule placement in dHC (Fig. 1B).

### 3.1. Postmeal inhibition of dHC glutamatergic neurons increases future intake in a time-dependent manner

Rats consumed similar amounts of the saccharin solution during their first meal in the three experimental conditions ($X^2(14) = 2821$, $p = 0.244$; Fig. 2B). Importantly, postmeal inhibition of dHC glutamatergic neurons significantly influenced the amount consumed during the second meal ($X^2(14) = 13.379$, $p = 0.001$; Fig. 2C). Post hoc tests indicated that IMMEDIATE postmeal inhibition increased the amount consumed during the second meal compared to intake on a day when the rats were not given any inhibition (NONE, $p = 0.002$; Fig. 2C) or given DELAYED inhibition ($p = 0.032$; Fig. 2C). In contrast, the DELAYED inhibition did not affect the amount of saccharin solution consumed during the second meal because the size of the second meal did not differ significantly between the DELAYED and NONE conditions ($p = 1.0$; Fig. 2C). Inhibition also increased the likelihood that rats would consume a second saccharin meal in a time-dependent manner ($X^2$ (2, $N = 15$) = 8.88, $p = 0.012$; Fig. 2D). Specifically, rats were more likely to consume a second meal when IMMEDIATE postmeal inhibition was given than when dHC neurons were not inhibited ($p = 0.016$; Fig. 2D), but DELAYED inhibition did not have this effect ($p = 0.687$; Fig. 2D). Indeed, 100% of rats consumed a second meal when IMMEDIATE inhibition was given.

## 4. Discussion

The present findings show that inhibition of dHC glutamatergic neurons given after the end of a meal caused all rats to consume a second meal during the experimental period and increased the amount ingested during that second meal when the neurons were no longer inhibited. Importantly, delayed postmeal inhibition did not have this effect. Our previous electrophysiological results indicate that neural activity returns to baseline immediately upon termination of the 10 min of inhibition (Hannapel et al., 2019), supporting the inference that neural activity was not inhibited during intake of the second meal in the present work. Combined with our prior evidence that inhibition given preceding or during intake of a first meal does not affect the amount consumed during that meal or the next, the current work indicates that the neural activity in dHC glutamatergic neurons during the early postprandial period is critical for limiting future intake. Together, these data suggest that dHC glutamatergic neurons inhibit future intake by consolidating the memory of the preceding meal.

Several lines of evidence suggest that the ability of postmeal inactivation to increase subsequent feeding cannot be attributed to heating or to some other non-specific effects produced by the 10 min of photoillumination. For instance, we have shown that postmeal pharmacological inhibition of dHC neurons using the GABA-A agonist muscimol has a similar effect on feeding (Henderson et al., 2013). More importantly, we showed previously that photoillumination of a control virus in dHC for the same duration did not affect feeding behavior when given before, during, or after a meal (Hannapel et al., 2019). The present findings replicate our previous optogenetic results indicating that postmeal inhibition increases future eating and advances knowledge by delineating the consolidation window for this effect. Indeed, the finding that the effects of the postmeal inhibition were time-dependent also argues against a heating effect. That is, using a within subject design, rats were given both immediate and delayed postmeal photoillumination on separate days and yet only the immediate manipulation increased subsequent intake.

Saccharin served as the meal in the present experiment to avoid the possibility that any time-dependent effects of postmeal inhibition could be due to the timing of interoceptive visceral cues generated by the meal. Our previous research found that saccharin ingestion increases dHC expression of *Arc* mRNA (Henderson et al., 2016) and that postmeal optogenetic inhibition of dHC glutamatergic neurons increased subsequent intake of a saccharin solution when the neurons were no longer inhibited (Hannapel et al., 2019). This suggests that the ability of dHC neurons to control future intake does not require postprandial interoceptive visceral signals because saccharin meal timing and size are determined primarily by oropharyngeal processes (Kushner & Mook, 1984; Renwick, 1985, 1986; Sclafani & Nissenbaum, 1985).

The current results are in concert with several previously published findings showing that dHC neurons are involved in memory consolidation in a time-dependent manner (Izquierdo et al., 1992; Jerusalinsky et al., 1992; Lorenzini et al., 1996; Oliveira et al., 2010; Riedel et al., 1999). The present findings suggest that the consolidation period for the memory of a saccharin meal is much shorter than that seen with other kinds of behavioral tasks, particularly those that are aversively motivated. For instance, dHC infusions of an AMPA receptor antagonist given immediately, 90 or 180 min after inhibitory avoidance training impair retention performance tested 24 h later (Jerusalinsky et al., 1992). It may not be surprising, though, that the consolidation period for saccharin is less than 80 min given that the average postprandial intermeal interval for saccharin is 90 min, and thus the duration of inhibition of subsequent intake is relatively brief (Hannapel et al., 2019). It would be interesting to determine in the future whether the consolidation period for a chow or 32% sucrose meal is longer given that the average postprandial intermeal interval for sucrose ingestion is 90 min (Hannapel et al., 2019; Henderson et al., 2016; Henderson et al., 2013) and for chow is 3 h (Snowdon, 1969). If that is the case, then it would suggest differences in the molecular mechanisms underlying the consolidation of each type of meal that could be further used to tease apart these different types of memory consolidation. Future research should also investigate whether specific hippocampal subfields (i.e., dentate gyrus, CA1- CA3) are critical for dHC control of future eating behavior.

In conclusion, the results of the current report show that glutamatergic dHC neural activity is necessary temporarily during the early postprandial period for limiting future intake. These results are consistent with the hypothesis that these neurons inhibit future intake by consolidating the memory of the preceding meal. To the best of our knowledge, our research group is the first to perform postmeal manipulations, allowing us to show that postmeal inhibition of dHC neurons increases future energy intake and implicate dHC glutamatergic neurons in the ability of meal-related memory to inhibit future intake in a time-dependent manner. We owe an incredible debt of gratitude to James McGaugh for this, and we are also thankful for his enduring mentorship and inspiration.

## CRediT authorship contribution statement

**S.B. Briggs:** Conceptualization, Formal analysis, Investigation, Writing - original draft, Visualization, Project administration. **C.B. Ware:** Investigation, Writing - original draft. **K. Sharma:** Investigation, Writing - original draft. **S.C. Davis:** Investigation, Writing - original draft. **R.T. Lalumiere:** Conceptualization, Writing - original draft, Funding acquisition. **M.B. Parent:** Conceptualization, Formal analysis, Writing - original draft, Supervision, Funding acquisition.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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